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Part II

Environmental Protection Agency

Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules

Good Laboratory Practice Standards for Health Effects

ENVIRONMENTAL PROTECTION AGENCY

[40 CFR Parts 770, 771, and 772]

Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules

AGENCY: Environmental Protection Agency.

ACTION: Proposed rule and notice of public meetings.

SUMMARY: This action proposes test standards for the development of data on the chronic health effects of chemical substances and mixtures for which testing will be required under the Toxic Substances Control Act (TSCA). With this proposal, the Environmental Protection Agency (EPA) initiates the process to codify these standards for incorporation into future TSCA Section 4 test rules. The Agency may also use these standards to respond to Section 4(g) petitions for test standards for new chemical substances. This proposal provides standards for testing for oncogenic (tumor-inducing) effects, other (non-oncogenic) chronic effects, and combined oncogenic and non-oncogenic chronic effects, by prescribing standards relating to experimental design, the conduct of tests, data evaluation, and other test requirements.

EPA proposes these test standards under Section 4(b) of TSCA. The ultimate purpose of the proposed standards is to assure that data developed under Section 4 test rules can be used by EPA to determine whether the tested chemicals present an unreasonable risk of oncogenic or other chronic effects and to support regulatory actions to eliminate or reduce such risk. The standards proposed at this time pertain to general provisions for the conduct of long-term laboratory animal bioassays. This proposal does, however, include general provisions that would apply to all TSCA health and environmental effects test rules. Standards for Good Laboratory Practices are also proposed in a separate part of today's **Federal Register.**

The Agency recognizes that long-term health effects testing is expensive and time-consuming. Estimates of the costs of performing tests in accordance with these proposed standards are presented in Section VI of this preamble. TSCA requires EPA to be selective in designating chemicals to be tested and in specifying the tests to be performed. Thus, to conclude from this proposal that large numbers of chemicals will routinely be subject to both oncogenic and non-oncogenic testing in accordance with the proposed standards would be erroneous and would give a misleading impression as to the likely economic impact of the TSCA testing program. Even so, the Agency is interested in ways of reducing the cost of performing oncogenic and non-oncogenic effects testing, insofar as the costs can be reduced without significantly impairing the reliability of test results and their usefulness for hazard assessment. EPA therefore will welcome and carefully consider suggestions for reducing costs.

DATES: Interested persons are invited to submit written comments to the EPA on these proposed test standards prior to the close of business on or before August 7, 1979. See section VII, Public participation, for further information.

PUBLIC MEETINGS: EPA has scheduled public meetings on these proposed standards. These meetings will be held during the week of July 9 in Chicago and during the week of July 16 in Washington, D.C. Additional information on these meetings incuding dates, times and locations, is presented in Section VIII, Public Meetings.

ADDRESSES: Written views and comments should bear the document control number OTS No. 046003 and should be submitted to: Ms. Joyce A. Barbour, Chemical Information Division, Office of Toxic Substances (TS–799), Environmental Protection Agency, 401 M Street SW., Washington, DC 20460.

FOR INFORMATION CONTACT: Industry Assistance Office, Office of Toxic Substances (TS–799), Environmental Protection Agency, 401 M Street, SW., Washington, D.C. 20460, Telephone No.: 800–424–9065 (toll-free) (In Washington, DC, call 544–1404).

SUPPLEMENTARY INFORMATION: A Support Document which provides the scientific bases for the test standards and discussions related economic and confidentiality issues is available upon request from the Industry Assistance Office, Office of Toxic Substances (TS–799), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. The Support Document must be read together with the preamble to obtain a complete explanation of the basis of this rule.

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I. Introduction

Under Section 4(b) of the Toxic Substances Control Act (TSCA) (Public Law 94–469; 90 Stat. 2006; 15 USC 2603), the EPA proposes standards for testing chemicals for chronic health effects. The proposal includes standards for long-term animal bioassays to test for oncogenic effects, and other (non-oncogenic) chronic effects. In addition to the standards proposed here, the Agency is also proposing standards for Good Laboratory Practices in a separate part of today's **Federal Register.**

Later this year, the Agency will propose the first chemicals to be tested in accordance with Section 4 test standards. In the present rulemaking to codify test standards, the issues center on the suitability of the proposed generic standards for testing chemicals under future Section 4 test rules. In later rulemakings to identify chemicals for testing, the issues will center on the need to test the identified chemicals.

When EPA determines that chemicals satisfy the testing prerequisites in Section 4(a), these chemicals will be joined in Section 4(a) test rules with the standards finalized as a result of today's proposal, or with revisions or modifications of these standards, as necessary and appropriate.

This preamble outlines EPA's legal authority to require testing of chemicals in accordance with test standards, discusses the use of test data for assessing the risk potential of toxic chemicals, and introduces the first Section 4 test standards to be proposed under TSCA.

Statutory Framework

General.—Section 4 of the Toxic Substances Control Act authorizes the Administrator of the Environmental Protection Agency to require manufacturers (including importers) and processors of identified chemical substances and mixtures to test the chemicals in accordance with applicable EPA test rules (Section 4(a), (b)). This regulatory authority implements Congress' stated intent that "adequate data should be developed with respect to the effect of chemical substances and mixtures on health and the environment and that development of such data should be the responsibility of those who manufacture and those who process such chemical substances and mixtures" (Section 2(b) (1)).

TSCA states that each Section 4(a) test rule must identify the chemical substances and mixtures for which testing is required, provide standards for the development of test data ("test standards"), and, for chemicals which are not new chemicals, designate deadlines for the submission of data developed under the rule (Section 4(b)(1)).

In today's action, EPA proposes test standards for oncogenic effects, non-oncogenic chronic effects, and combined chronic effects. In future actions, EPA will propose Section 4(a) test rules which identify specific chemical substances and mixtures which are to be tested, give deadlines for the submission of test data to the EPA, and specify the persons (Sponsors) who are required to conduct tests and submit data to the Agency. The Sponsor(s) may be the manufacturer(s), processor(s), or both, of the specified chemical.

Test standards.—TSCA specifies that each test rule must include standards for the development of test data. The test standards must prescribe the health and environmental effects, and the information relating to toxicity, persistence, and other characteristics which affect health and the environment for which test data for a chemical substance or mixtures are to be developed, and any analysis that is to be performed on such data (Sections 4(b)(1) and 3(12)(A). The Act states that carcinogenesis mutagenesis, teratogenesis, behavioral disorders, cumulative or synergistic effects and any other effect which may present an unreasonable risk of injury to health or the environment are effects for which test standards may be prescribed (Section 4(b)(2)(A)). The Act further specifies that the characteristics of chemical substances and mixtures for which such standards may be prescribed include persistence, acute toxicity, subacute toxicity, chronic toxicity, and any other characteristic which may present such a risk (Section 4(b)(2)(A)).

In addition, to assure reliable and adequate data for such health and environmental effects, each test rule must include standards which prescribe the manner in which data are to be developed, any test methodolgy to be employed in the development of such data, and such other requirements as are necessary to provide such assurance (Sections 4(b)(1)(B) and 3 (12)(B)). The Act specifies that the methodologies that may be prescribed in such standards include epidemiological studies, serial or hierachical tests, *in vitro* tests, and whole animal tests (Section 4(b)(2)(A)).

Chemical identification.—In order to require that a chemical be tested in accordance with EPA test standards, the Administrator must make three findings relating to the chemical's risk potential and the insufficiency of data then available to EPA.

First, the Administrator must find either that the manufacture, distribution in commerce, processing, use, disposal, or some combination of these activities involving the chemical may present an unreasonable risk of injury to health or the environment, or that the chemical is or will be produced in substantial quantities and that there is or may be significant or substantial human or environmental exposure to the chemical (Sections 4(a)(1)(A)(i) and (B) (i)).

Second, the Administrator must find that existing data and experience relating to the chemical are insufficient to reasonably determine or predict the effects on health or the environment of the manufacture, distribution in commerce, processing, use, or disposal of the chemical or of any combination of these activities. (Sections 4(a)(1)(A)(ii) and (B)(ii)).

The third finding is that testing is necessary to develop the requisite data (Sections 4(a)(1)(A)(iii) and (B)(iii)).

Section 26(c)(1) provides that any action authorized or required under any provision of the Act with respect to a chemical substance or mixture may be taken with respect to a "category of chemical substances or mixtures." Section 26(c)(2)(A) explains that the term "category of chemical substances" means a group of chemical substances the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or the environment, or the members of which are in some other way suitable for classification as such for purposes of the Act, except that such term does not mean a group of chemical substances which are grouped together solely on the basis of their being new chemical substances.

The Administrator may require testing of mixtures only if, in addition to the foregoing findings, he finds that the necessary information cannot reasonably and more efficiently be obtained by testing the separate components in the mixtures (Section 4(a)(2)). Also, chemicals manufactured, processed, or distributed in commerce for use as pesticides, food additives, drugs, and cosmetics are among the chemicals to which TSCA, including the testing authority, does not generally apply (Section 3(2)(B)). However, such chemicals may be tested under Section 4 if they are also manufactured, processed, or distributed in commerce for other uses not excluded from TSCA authority.

Relation to premanufacture notification.—Under Section 5 of the TSCA any person who intends to manufacture a new chemical substance for commercial purposes in the United States must submit a notice to the EPA at least 90 days before such manufacture (or import) commences. The person must describe intended production, use and disposal plans, data on chemical and biological properties, and other information relating to the new chemical substance (Sections 5(a), (d)(1)). On January 10, 1979, the Agency proposed regulations and forms to implement the Section 5 notification requirements (44 FR 2242). The preamble to that proposal reviews the relevant statutory provisions and discusses the Agency's plans for implementation of Premanufacturing Notification.

The notification requirements in Section 5(b)(1) and the categorization authority in Section 26(c) require manufacturers of new chemical substances that are in a category for which testing is required under Section 4, to conduct the tests required for the category and submit the data with the premanufacture notification form. Specifically, Section 5(b)(1) provides that if a person is required both to submit a premanufacture notice to the Administrator and to submit test data for the substance under a Section 4 rule, the person must submit the data in accordance with the rule at the time the premanufacture notice is submitted.

In addition, persons intending to submit a Section 5 Premanufacture Notice but who are not subject to a Section 4(a) test rule may petition the

Administrator to prescribe standards for the development of test data for such substance (Section 4(g)). The Administrator must either grant or deny the petition within 60 days and, if a petition is granted, the Administrator must prescribe standards within 75 days of the date the petition is granted.

Applicability of test standards.— Section 4(b)(3)(B) specifies that if the Administrator makes the Section 4(a) findings referenced in that section (See discussion of chemical identification, above), the relevant test rules apply to each person who manufactures or intends to manufacture, and/or to each person who processes or intends to process the chemical substances and mixtures for which test data is required. The section also provides that the Administrator may permit two or more of the manufacturers and/or processors who are required to conduct tests and submit data to the EPA to designate one such person or a qualified third person to conduct the tests and submit such data on behalf of the persons making the designation. Because TSCA defines "manufacuture" to include "import into the customs territory of the United States" (Section 3(7)), the term "manufacturer" is used to mean both manufacturers and importers in this preamble and in Section 4 test rules.

Under Section 4(c) any person required by a section 4(a) test rule to conduct tests and submit data may apply to the Administrator for an exemption from such requirement. If the Administrator determines that a chemical substance or mixture for which an exemption application was submitted is equivalent to a chemical substance or mixture for which data have been submitted to the Administrator under a Section 4(a) rule or are being developed under such a rule, and that submission of data by the applicant would be duplicative of data which have been submitted to the Administrator under a Section 4(a) rule or are being developed under such a rule, the Administrator shall exempt the applicant from conducting tests and submitting data (Section 4(c)(2)). In accordance with procedures and rules authorized but not yet implemented by Sections 4(c)(3) and 4(c)(4), those persons exempted from conducting testing and submitting data must reimburse those persons submitting the data on which the exemption was based.

Implementation

The Administrator will propose chemicals to be tested for chronic effects when the Agency has determined that such data are necessary to adequately assess whether or not the chemical(s) may present a risk of injury to human health.

Except as provided below, each proposed test rule which identifies chemicals for chronic toxicity testing will reference the appropriate test standards finalized through the rulemaking which this proposal initiates. The Administrator may proposed individualized modifications of these standards for certain chemical substances and mixtures. Also, TSCA requires the Administrator to review the adequacy of these test standards at least once each year and, if necessary, to institute appropriate proceedings to revise the standards (Section 4(b)(2)(B)).

Each proposal which identifies chemicals for testing will: specify the chemical and physical form of the chemical for which testing is required, give deadlines for the submission of data to EPA, specify the persons (manufacturers, processors, or both) who are required to conduct the tests and submit data to EPA, provide other information necessary to conduct the required tests, e.g., route of exposure, and any necessary modifications to the standards.

When persons intending to manufacture or process new chemical substances submit Section 4(g) petitions for chronic effects test standards, the Agency will prescribe the standards finalized through this rulemaking or modifications of these standards, as appropriate.

The Agency will generally use the legal authority and approach outlined in this section in developing other TSCA test rules. The legal authority for other aspects of Section 4(a) test rules and related EPA action will be detailed when those rules and related procedures are published.

II. Basis and Purpose

People are afflicted with a wide variety of chronic diseases, including various types of cumulative effects which impair organ functions and neoplasias. Among these chronic effects are lung conditions, such as chronic bronchitis, pneumoconiosis, and emphysema; chronic liver disease, such as cirrhosis; chronic kidney disease, such as nephrosis and chronic interstitial nephritis; chronic nervous conditions, such as impaired mental or motor activity, and neuropathies; chronic skin effects; bone demineralization; cataracts; hematopoietic and cardiovascular conditions and generalized emaciation and debilitation. Malignant neoplasias represent one particularly large group of over 200 different disease processes described generally as "cancer".

Because of the broad spectrum of human susceptibility, chronic diseases produce mild to severe health effects in humans of all ages, races, and nationalities, regardless of sex. Most of these conditions adversely affect the quality of life for the affected person and his or her family, impose significant health care costs, restrict employability and other normal activity, and reduce life expectancy.

The exact cause of a chronic disease is often difficult to determine for each individual. However, environmental agents such as radiation, viruses, and chemicals have been identified as potential factors in the etiology of many chronic diseases. Numerous studies have demonstrated a higher incidence of particular chronic conditions in human populations exposed to certain chemicals, especially those in the workplace. The same chronic diseases occurring in the general population may also be related to specific chemical exposure.

Because chronic disease is a major human health problem, the Agency proposes test standards for developing experimental animal data that would be used to assess the risks of chemically-induced chronic health effects in humans. The standards serve several different purposes in relation to this risk assessment objective.

First, testing in accordance with these standards would permit a determiniation of whether the chemical produces particular effects such as kidney damage, liver damage, or tumors in test animals. Second, the standards are designed to develop data of a kind and quality that will permit an estimate of the probable magnitude of harm to humans who may be exposed to the chemical. This information along with other considerations would permit the Agency to decide whether any regulatory action is appropriate. Finally, because the standards are designed to assure that test data are reliable and adequate for risk assessment purposes, the Agency, industry and the public would be confident that these data are reliable indicators of the nature and extent of the risk and that the Agency's regulatory decisions are based on sound data. When these test data indicate that the chemical may present a risk of injury to human health, the Agency will review that data in terms of regulatory measures available under Sections 5, 6, 7, and 9 of TSCA.

The Agency has selected long-term bioassays as the method for development of chronic health effects

test data. Long experience has established that such bioassays provide toxicity data of the kind and quality required for chronic effects hazard evaluation. Such bioassays have predicted or confirmed the carcinogenic potential for chemicals such as vinyl chloride, benzidine, 4-aminobiphenyl, bis(chloromethyl)ether, diethylstilbesterol, beta-naphthylamine, aflatoxin, and asbestos which are now widely accepted as carcinogens in humans. Data from animal bioassays have provided valuable data on which to base regulatory actions to restrict the use of these injurious chemicals and thereby reduce the risk to humans.

The importance and utility of long-term animal bioassays for development of test data on chronic health effects stems in part from the limits on other approaches to the development of such data. For example, in many cases, human studies cannot be conducted for ethical or legal reasons or because of scientific considerations such as the inability to identify a population that has been exposed to the chemical under conditions that permit meaningful scientific analysis.

Morover, even when such populations can be identified, it has been difficult, or in some cases impossible, to confirm by studies of humans a direct association of exposure to a specific chemical substance with a chronic disease. This is primarily due to: the long latency period (10–30 years in humans) for manifestation of many chronic disease states, exposure to several substances during that period, the inadequacy of personal histories or records on exposure to specific substances, concomitant factors such as smoking, malnutrition, infectious diseases, and genetic defects, and the great expense to conduct epidemiological studies having sufficient populations to demonstrate effects.

Thus, because epidemiological information is often impractical or impossible to apply to particular chemicals, such studies cannot always serve as a general methodology for ascertaining their chronic toxicity potential. When epidemiological data are available, they are often the best evidence for the identification of risk factors and hazardous processes that may result in excessive mortality rates. However, in the absence of such data, long-term animal bioassays provide the information necessary for this purpose.

III. Proposed Test Standards

General

This section of the Preamble summarizes the scientific base for the proposed test standards and reviews alternatives that the Agency considered. These issues are addressed in greater detail and with references in the Support Document for the proposed test standards. The proposed test standards have been modeled after generally accepted testing methodology and formulated on the basis of critical review by Agency scientists in consultation with scientists in industry, government, and universities.

Summary of Standards

The proposed test standards would require Sponsors to administer test chemicals to both sexes of at least two (2) species of laboratory animals, from weaning until 24–30 months of exposure and examine all animals in the study at their death for gross and microscopic abnormalities. There are some variations to the standards, depending upon the particular test to be conducted. The main differences are in number and types of species, doses and dose levels, duration of the tests and the extent of microscopic examination of tissues. For example, mice and rats are to be used in the oncogenic effects test, whereas rats and a non-rodent species are used in the test for other chronic effects. The combined test employs all three species. The number of doses varies with the particular test—three (3) for both the oncogenic effects test and for the non-oncogenic chronic effects tests, and either 3, 4 or 5 for the combined test, depending upon the species and the chemical. The proposed requirements for microscopic examination of tissues are more extensive in the chronic and combined chronic tests than in the oncogenic effects test. In addition to experimental design aspects, standards are proposed for the diet, chemical analysis, clinical examinations and scientist and technician qualifications.

Under these standards, persons subject to TSCA chronic effects test rules would develop and submit to the Agency the following kinds of information:

(a) Information relating to test methodology such as species tested, duration of test, exposure route(s), dose levels, clinical/pathological examinations, and any other methodological considerations prescribed in § 772.113 of this proposal;

(b) Information and data derived from these procedures such as data on the incidence of gross and microscopically-detected tumors or other lesions by species, sex, dose level, time on study, and data on clinical test results, and any other data and observations that relate to the chronic effects of the chemical in test animals;

(c) Information relating to Good Laboratory Practices such as nature and purity of the test substance, and qualifications of personnel conducting the tests, and other data prescribed in § 772.110–1.

(d) Analysis of data developed in the study, data describing deviations and departures from the prescribed protocols, and other factors which require qualification of the data or otherwise limit the interpretability of the data.

Definitions

"Chronic" effects refer to disease processes which have a long latency period for development, result from long-term exposure, are long-term illnesses, or combinations of these factors. Certain chronic effects, such as tumors or life-shortening, generally become manifest late in life regardless of the exposure. Other chronic effects, such as liver or kidney damage, may be similar to acute or subchronic effects observed after short-term exposures. They appear as chronic effects under conditions of less intense but longer exposure which might result in a gradual accumulation of tissue damage to the point that the effect eventually becomes manifest as an organ dysfunction. Oncogenic effects represent one major type of chronic effect requiring special considerations and thus separate standards are proposed.

The best standards for neoplasia, or tumor induction, are called "oncogenic" effects test standards rather than "carcinogenic" test standards, the term often used in the past. By strict definition, carcinogenicity pertains to invasive (or malignant) neoplasia arising from epithelial cells. The term oncogenicity includes the disease processes that result in benign and/or malignant neoplasms of any cell type and, thus, is considered the more appropriate term for these test standards.

Although the histogenesis of many benign neoplasms, and their eventual fate, is not fully known, medical scientists generally view benign neoplasms as significant because certain "benign" tumors may have serious consequences, including transformation to malignancy. For example, gliomas, benign brain tumors, and benign liver and kidney tumors

often result in death or require radical surgical treatment.

Thus, these standards define an "oncogen" as a chemical agent that either initiates, promotes, or causes biologic changes that result in benign and/or malignant neoplasms.

Submission of Study Plan

The standards propose submittal of a Study Plan ninety days prior to initiation of the chronic test(s). The submission of a Study Plan prior to test does not and should not be taken to mean that the Agency intends to approve or disapprove the Study Plan. Submission of the Study Plan will allow the Agency to become knowledgeable about the tests to be undertaken, facilitate discussion and approval of certain Sponsor-recommended modifications, and aid in the determination of exemption requests filed under Section 4(c). A list of information items to be included in the Study Plan is contained in § 772.113–1.

Personnel Qualifications

Perhaps the most critical element in the design and conduct of chronic effects studies is that of having knowledgeable and motivated scientific staff managing and conducting the studies. The Agency, in attempting to arrive at a means of assuring reliable data, proposes certain qualification requirements in the standards for key scientific staff. Considered especially critical are the Study Director, and the responsible toxicologist, pathologist veterinarian, and histology and animal technicians. Other disciplines are also important, e.g., chemist, biochemist, and statistician. However, it is expected that the Study Director and Sponsor will assure the qualifications of all disciplines and the performance of all aspects of the studies. Standards for the Study Director are contained in the standards for Good Laboratory Practices, § 772.110, while standards for the pathologist, veterinarian, and technicians are contained in § 772.113–1.

The Agency recognizes the possible shortage of experimental pathologists having the qualifications defined in the standards and available to conduct routine diagnostic pathology, but, it also realizes the effects on decision-making of a less than adequate examination. The Agency is concerned with the lack of confidence in the routine diagnostic pathology carried out by unqualified pathologists. The standards propose that the responsible pathologist must be a board-certified or board-eligible medical or veterinary pathologist, with at least three years experience in pathology of the species to be examined. Other pathologists with less experience, can work under the direction of the responsible pathologist. Parapathologists, i.e., persons that have received special training in histology and gross necropsy, but do not possess a medical sciences degree, are not considered as having adequate academic training to conduct diagnostic microscopic examinations. The differentiation between normal tissues and many lesions, the diagnoses of these lesions, and an assessment of their biological nature, often requires a high degree of professional judgment. An ability to make such judgments can be attained only by a combination of intensive medical training and practical experience. It is acknowledged that there may be laboratories where parapathologists are well-trained and closely supervised who are employed satisfactorily in sorting or screening abnormal from normal tissues. Such situations, however, are considered rare and difficult to evaluate; therefore, the test standards do not permit the use of parapathologists for final microscopic diagnoses.

In arriving at these proposed standards for pathologists, the Agency realized that no simple definition would satisfy all situations, e.g., where pathologists are on a satisfactory consulting or subcontracting arrangement. The Agency is also aware that studies may be conducted in foreign laboratories. Some American and foreign pathologists may indeed be "qualified" but do not possess the proposed standards requirements. On the other hand, it is possible that a few pathologists, meeting the proposed standards, may not be considered "qualified" by their peers.

The Agency is also proposing standards which require that a veterinarian certified or eligible for certification in the American College of Laboratory Animal Medicine and having at least two years experience with the animal species to be used must be in charge of animal care and welfare. This requirement is proposed because Agency experience has shown that poor animal care has led to erroneous and useless experimental data. In order to assure reliable data, the Agency is thus proposing specific qualificaitons for the veterinarian in charge. The resource limitations do not appear as critical for the animal care veterinarian as in the case of the responsible pathologist.

The Agency is not proposing criteria for the responsible toxicologist at this time although that is under consideration. The reason for this is, in part, that there had not been a board for general toxicology until 1979. Only recently, the Society of Toxicology has created the American Board of Toxicology Certification. When the certification process has developed a suficiency of certified toxicologists, the agency may want to require such certification as a requirement for the toxicologist in charge of the studies conducted under section 4 test rules. There have been other toxicology boards for several years, e.g., veterinary toxicology, medical toxicology, and forensic toxicology; however, these specialty boards have not been related to general toxicology. For this reason, the Agency thinks that certification in those boards would not be an appropriate requirement for Section 4 activities.

The Agency is particularly interested in viewpoints as to how best to achieve the degree of personnel qualifications needed for these chronic studies while allowing for the use of adequately trained and experienced scientists that have equivalency in capabilities. This issue is of special concern regarding foreign conducted studies.

Chemical Analyses

Section 772.113–1 proposes that certain chemical tests be performed to determine: a) the stability of the test substance in the test mixture, b) methods to assure homogenous mixing of the test substance in the test mixture (feed or other carrier material), and c) concentration of test substance in each test mixture. The test standards would require chemical analyses which are intended to provide reasonable assurance that the test mixture contains the requisite level of test substance and that it is mixed equally throughout. Ideally, the test mixture to be administered to the test animals should contain the exact amount of the dose planned for, without any degradation impurities and with complete homogeneity of the test substance in the mixture.

The need for stability studies is prompted by the fact that some chemicals degrade or are lost from the mixture due to volatilization and/or elution from the mixture. As the rate of loss varies with the chemical and storage conditions of the test mixture, exact requirements for method of storage and period for use of the test mixture are not practical. The need to achieve homogeneity is so that all animals receive the exact same dose rather than a range of doses that might occur with a non-homogeneous mixture. From the practical standpoint, this is

often difficult to achieve, especially with some chemicals that do not mix well at low levels. Due to the need to vary the extent of chemical analyses and mixing/storage procedures with the test chemical, the Agency proposes performance standards leaving the determination of methods to achieve them up to the Sponsor.

Dietary Considerations

The diet is a very significant source of variance in long-term studies. The longevity of several animal species, including humans, has been shown to be influenced considerably by the quality and quantity of the diet. It is essential that a nutritionally adequate diet that meets the needs for long-term animal health be utilized. In addition, the presence of dietary contaminants has been suggested as a major contributory factor in the outcome of long-term studies in that they may influence the incidence of lesions in test animals and make assessment of the causative relationship uncertain. For these reasons, the Agency proposes a specific diet for use in long-term studies as well as standards for chemical analysis for nutrients and dietary contaminants. Concern for the availability of the proposed diet prompted inquires to the National Institutes of Health and commercial laboratory feed companies. The Agency believes that the specified diet can be obtained by the Sponsor without substantial increased cost or time delay. Comment is specifically requested on the question of the benefits and problems associated with the requirement of a specific diet, and whether similar quality control can be assured through other means.

Reporting Requirements

As the purpose of Section 4 test rules is to develop data which can be utilized in assessing risk from the test chemical, the Agency proposes an extensive list of data items to be reported in the final test report. These relate to test procedures, conduct of the study, results, and analyses of the results.

It is anticipated that the Agency will require that the final report of a Section 4 test contain an abstract, introduction, methods and materials, results, discussion and data analyses, conclusions, and references, as well as formatted in a specified manner. The Agency intends to propose specific standards for data formatting later this year. Standardized formats will facilitate study comparisons and a more efficient review of test data submitted under Sections 4 and 5 of TSCA. The Agency is also considering the use of electronic data processing techniques to manage the large quantities of data that may become available through the implementation of TSCA, and may provide guidance on the use of such techniques in that context.

It is also proposed that Summary Reports be submitted on a quarterly basis which would provide the current status of the study. It is expected that these interim summary reports will be brief (5–10 pages) and provide summary information on significant findings of such parameters as survival, weight changes, clinical test results, accumulative incidence of tumors and toxicity.

Animal Selection

The Oncogenic Effects Test Standards propose the use of rats and mice, whereas the Non-Oncogenic Chronic Effects Test Standards propose the use of the rat and non-rodent. The Combined Chronic Effects Test Standards propose three species, the mouse, rat, and a non-rodent. Alternate species will be considered by the Agency on a case-by-case basis. Both sexes are proposed for all three standards.

For Oncogenic Effects Test Standards: Rats and mice have been found to be reliable models for human oncogenicity. Virtually all confirmed human oncogens, with the exception of arsenic, also are oncogenic in these species. Furthermore, since much oncogenicity testing has been done with rats and mice, these prior results provide a reference for new tests results. The choice of rodents is based also on economic and time concerns. In order to develop statistically meaningful data, large numbers of animals usually are required. The cost to conduct studies with large numbers of rodents is considerably less than that involved in the use of large numbers of large animals, such as dogs or monkeys. A second factor, that of the long latency period for tumor development, requires that animals be exposed and/or observed for most of their normal lifespan. Whereas with rodents this period is 2–3 years, dogs and monkeys must be maintained for 7–10 years. Not only does this greatly increase the cost, it means that the data will not be available for the correspondingly longer period.

In certain cases there may be a scientific rationale for using a different species, e.g., one having more comparable metabolism to that of humans. Where such a rationale exists, the Agency will consider permitting use of an alternate species.

Two species are proposed because in the past, chemical oncogens have not always proven positive in one species while positive results have been found in other species. Similar results in both species markedly increase the degree of confidence when extrapolations are made to humans. Data from a second species are particularly important when a chemical appears to be non-carcinogenic in the first species tested. Both sexes of both species are proposed because of the previously demonstrated differences in response of female and male animals to various chemicals in oncogenicity testing. In many previous oncogenicity tests neither the more sensitive sex nor species could have been predicted.

For Non-Oncogenic Chronic Effects Test Standards: Rats and a non-rodent (usually dog) are required. The basis for this is that non-oncogenic chronic effects are sometimes detectable in non-rodents but not in rodents (or vice versa). Another reason for the non-rodent is the enhanced capability to conduct more precise clinical evaluations with larger animals.

The Agency has received conflicting viewpoints as to the practicability of proposing a non-rodent species in addition to a rodent species for chronic effects testing. Those challenging the need for a non-rodent contend that nearly all chronic effects will be observed in the rodent, except in those instances in which species differences in metabolism, transport mechanisms, and/or protein binding might occur. Exposure levels for effects might differ and thus the basis for establishing exposure limits, e.g., Average Daily Intakes (ADI's) or Threshold Limit Values (TLV's), will be better than if only rodent data is available. Generally, dose-related effects obtained with larger animals more nearly approximate those expected in humans. As the Agency will likely propose exposure limits for chemicals tested under Section 4, where positive test results are found, dose-response data with two species will provide a firmer scientific basis for the risk estimations that might result.

Dogs have been extensively used as the usual non-rodent species of intermediate lifespan between humans and the common laboratory rodents and they are of a convenient size disposition for clinical examinations. In addition, they are relatively easy to breed and are available in relatively large numbers and of genetic similarity (if purebreds are desired). Non-human primates have also been promoted as surrogates for humans based primarily upon their phylogenetic relationship and similarity

in physiological functions. They are generally difficult (and expensive) to obtain in a defined (disease-free) condition with most animal sources from foreign countries having restricted exportation quotas. For routine testing, the advantages of non-human primates over dogs likely do not offset the procurement, cost, and management problems involved in the use of primates.

For Combined Chronic Effects Test Standards: Three species, mouse, rat and a non-rodent are proposed in order to adequately assess both oncogenic and non-oncogenic chronic effects. In order to test the chemical for oncogenic effects in two species, both the rat and mouse must be used, as the duration of the non-rodent study would be too short due to a longer latency period for tumor development than the observation period. The non-rodent species is necessary to evaluate non-oncogenic chronic effects.

The Agency has not specified that a specific strain or stock of species be used as there are many strains which might be satisfactory with none clearly the preferred one for routine testing. Rather, the selection is to be made by the Sponsor of the test with the rationale to be presented at the time of Study Plan submission. In certain circumstances, the Agency might choose to propose a specific strain in the chemical test rule. Strains anticipated to be the most sensitive should be used unless a scientific basis exists for not doing so. The advantages of using inbred strains, hybrid strains, or an outbred stock are controversial. Inbred strains have less variability in biological characteristics such as average lifespan and spontaneous tumor rate and thus are more predictable in response. In contrast, outbred strains are generally more resistant to diseases and less likely to be genetically-resistant to a specific oncogenic agent. While the scientific community is divided as to the best choice for routine chronic toxicity testing, many scientific bodies consider the heterogeneity of response of outbreds as more likely to reveal an effect, and thus a characteristic that may outweigh the advantages of inbred strains. Hybrid strains possess many of the advantages of inbred strains while the increased gene pool lessens the probability of not responding due to strain-specific resistance. The National Cancer Institute uses a hybrid strain of mouse in its testing program primarily due to its hardiness (hybrid-vigor) and good longevity.

Use of Positive Controls

The Agency recognizes that to evaluate the validity of negative results it is important to be assured that the test animals are sensitive and respond to the chemical stimulus in a predictable manner. One way to determine such inherent sensitivity is to expose groups of the test animals to agents which produce the effect to be tested for. Such groups are known as "Positive Controls." Positive controls also have value in the monitoring of technical procedures and controls, such as diet mixture, pathology diagnoses, and data recording, as well as allowing comparison of research results within and between laboratories. The Agency is not proposing the routine inclusion of positive controls with each chemical test as they may not always be needed to adequately evaluate the sensitivity of the test animals. In addition, the Agency recognizes the technical and safety problems of employing known toxic chemicals in the laboratory. At the time of Study Plan submission the Sponsor should provide evidence which substantiates that sensitive animals are to be used. If this cannot be done, then positive controls may be needed. In certain cases, the Agency may include positive controls as a requirement in a specific chemical test rule.

Age at Start of Exposure

It is proposed to start animals on test at the earliest practical age, preferably immediately after weaning and acclimatization. This will be no later than six weeks of age for rodents and ten weeks of age for dogs. The sensitivity of the test system to detect chronic effects is enhanced if the animals are continuously exposed to the test substance from the period of rapid growth through adulthood.

The Agency considered providing for greater sensitivity in the Oncogenic Effects Test Standards by beginning exposure *in utero* and continuing it through the neonatal, infant, and adult life stages. The extent of the enhanced sensitivity is difficult to quantify. In studies using *in utero* exposure, tumors have been observed in organs other than those in which tumors were observed following adult exposure only. The Agency in not aware of any chemical found to be oncogenic as a result of *in utero* exposure that has not been determined oncogenic following post-parturition exposure alone; however, too few chemicals not oncogenic in adults have been tested by *in utero* exposure. Consequently, the data do not appear sufficient for deciding for or against the use of *in utero* exposure. Considerably greater cost and difficulties of adjusting exposure, litter randomization, etc., in using *in utero* exposure are significant considerations. However, the Agency invites comments on this issue.

Comments have been received that starting rodents on test at six weeks of age may be difficult to achieve, if animals must be obtained from a commercial supplier, acclimatized for 1–2 weeks and then subject to scheduling uncertainties within the laboratory. The Agency believes that six weeks is achievable except in rare situations. In those cases, the Sponsor should provide a rationale for starting at a different age.

Route(s) of Exposure

The Agency will designate route(s) of exposure individually for each chemical identified in each testing regulation. In general, the test chemical will be administered by the route(s) which simulates as nearly as possible the expected or known human exposure. Such experimental designs would provide greater confidence in extrapolating the test results to predict human hazards.

The most common human exposure route(s) may not always be the most important potential mode(s) of exposure. The kinetics of absorption and potential for local or systemic effects will be considered in selecting the route(s) of exposure to be used in the tests. For example, even though greater exposure to a chemical may be to the skin, if there is greater absorption through inhalation or ingestion, these routes may present the greater risk. In such a case, the Agency will likely propose testing by inhalation and/or ingestion. It is anticipated that usually only one route will be selected for testing; however, there may be occasions in which data obtained with two or more routes may be necessary to adequately assess for risk.

While the primary concern is for the development of the most meaningful data for assessment purposes, the Agency does recognize the necessity to consider resource availability and economic factors in selecting the route(s) of exposure for testing. For example, if both inhalation and ingestion routes would be expected to give equally meaningful results the Agency would probably select the less expensive route, ingestion. The Agency also realizes that certain aspects of testing may vary with the route of exposure, e.g., frequency of treatment, husbandry practices, and pathology. In those cases, the Agency may indicate such modifications in the test rule or

may accept modifications proposed by the Sponsor at the time of Study Plan submission.

Number of Animals

The number of test animals determines in part the sensitivity of the test, i.e. its ability to demonstrate the effect(s) studied and the reliability of the observed effects. The utility of the data for risk assessment purposes is therefore highly influenced by the number of animals studied. The proposal proposes a minimum of 50 rodents or six non-rodents for each exposure or matched control group, with a group consisting of one sex of one species at one dose level. Historically, this number for each group has been selected primarily because it represents a compromise between the desired sensitivity of the test system and economic or practical considerations. An additional group of eight rats/group are proposed for the non-oncogenic chronic effects and combined chronic effects standards for the conduct of clinical chemical analysis. Additional animals must also be used if interim kills are planned.

The Agency considered not specifying a minimum sample size for the oncogenic effects test standards, providing instead specified error rates, e.g., 95% probability of detecting a 10% increase in tumor incidence between chemically-exposed and control animals. The Agency recognizes, however, that in testing chemicals of unknown potential oncogenicity or chronic toxicity, the target organ is generally not predictable. Because the incidence of spontaneously occurring tumors or chronic conditions varies so widely among organs, calculating the number of animals based upon predetermined or specified error rates would be impractical in many cases. To achieve the same level of sensitivity given a high background incidence would require many more animals than if the background incidence was very low in controls.

Also considered was the use of an unbalanced design which would allow variation in the number of animals at different dose levels. This technique remains under consideration and the Agency requests comment on its scientific merit. The Agency also considered requiring fewer rodents for the Non-Oncogenic Effects Test Standards, but concluded that the foregoing considerations were equally applicable to testing for these other chronic effects.

Duration of Exposure/Observation Period

For Oncogenic Effects Test Standards: Since tumors have a long latency period, animals on oncogenicity tests must be allowed to live most of their life expectancy. The proposed Oncogenic Effects Test Standards propose that rodents be exposed to the test substance for a minimum of 24 months but no longer than 30 months prior to sacrifice. Continuous administration of the test chemical for this long exposure period should maximize the sensitivity of the test, thus enhancing the confidence in a negative test result. The Agency considers that with proper selection of rodent strains and proper husbandry practices, survival rates at 24 months in both rats and mice will be satisfactory for analysis purposes. Termination at 30 months is based upon the opinion that further continuation rarely would increase substantially the test sensitivity. In some cases it might tend to decrease the sensitivity as older animals die, or are cannibalized or autolyzed, and thus lost from the experiment.

The Agency has considered longer and shorter periods of exposure as well as the following alternatives to a prescribed exposure period: (a) continuous exposure until a predetermined level of mortality occurs, e.g., 75% of controls or of each test group, (b) continuous exposure until death of each animal, (c) set period of exposure followed by an additional period of observation, e.g., 18 month exposure and 6 months observation, (d) predetermined exposure period based upon expected length of life from literature information or historical control data.

A period of less than 24 months could decrease the sensitivity of the test to detect oncogenic effects. Certain tumors may have a long latency period and may be observed at 24 months but not at 18 months. The increased observation time will also increase the probability of detecting metastatic tumors. With current husbandry methods, rodents live longer than they did several years ago, and 24 months represents an achievable life expectancy for most strains. Alternatives (a) and (b) would assure that exposure was for the greater portion (or all) of the animals lifespan; however, these methods provide logistical difficulties in conducting the test and complexities in data analysis. Continuous exposure for the entire period is preferred over alternative (c) in that the test is often more sensitive. Historical control data, whether from within the test laboratory or from literature, is often unreliable for predicting the expected length of life, due to variables in breeder operations, seasonal fluctuations, etc. For this reason, alternative (d) was rejected.

For Non-Oncogenic Chronic Effects and Combined Chronic Effects Standards: In order to develop data suitable for evaluating life-shortening effects, as well as detect late occurring pathologic conditions, a period of at least 24 months for mice and non-rodents and 30 months for rats is proposed. While this period in non-rodents such as the dog or monkey may not be sufficient to detect life-shortening effects, it is expected that the vast majority of latent effects will be evident in high dose groups at that time. An even shorter period, such as 6–12 months, has also been considered for tests with non-rodents, especially the dog. EPA does not regard short periods as adequate because of the long latency period.

Dose Selection

For Oncogenic Effects Test Standards: The standards propose at least 3 dose levels of the test substance, with the High Dose Level (HDL) to be slightly toxic. The second dose is proposed to be a fraction of the high dose (generally ½ to ¼) with the low dose to be no more than ½ of the intermediate dose and no less than 10% of the high dose level selected. It is possible that some materials will have such a shallow dose-response curve for certain toxic effects, such that some toxicity might be observed at 10% of the High Dose Level. This is expected to occur only rarely. The proposal for a minimum of 3 dose levels is primarily to develop information as to the oncogenic potential of the tested agent although it should also indicate the general slope of the dose-response for the species responding. Such a design may not provide data sufficient for a precise dose-response analysis, and the Sponsor can add additional dose levels if desired to develop such information.

Determination of High Dose Level: In oncogenicity testing, the concept of employing high exposures, much greater than usual human exposure, is considered a valid procedure. This is based upon two factors: the statistical insensitivity of detecting an effect with small groups of animals and the possible differences in sensitivity between the test animals and humans. The probability that a test using small numbers of animals might detect a significant oncogenic response at the usual low, human exposure levels, is

minimal except for the most potent of oncogens. A chemical inducing tumors in ½ percent of the U.S. population would result in over a million cancer cases. Yet a true cancer rate as high as 10–11 percent will go undetected over 5% of the time in a group of 50 animals. In order to increase the sensitivity to detect an oncogenic response, either many more animals must be utilized at the lower exposures, or higher exposures must be employed. The only practical approach for a routine test for oncogenic potential is to use high exposures.

These standards refer to a High Dose Level rather than a "Maximum Tolerated Dose" (MTD) as used in some guidelines on oncogenicity testing. The difference in terminology reflects the Agency's concern with the confusion and misinterpretation of MTD, as in the past the maximum tolerated dose has rarely been tolerated, depending on one's interpretation of definition of tolerance. No objective criteria for tolerance for the MTD have been accepted by all investigators. The MTD frequently used in the past has resulted in some decrease in survival rate, weight decrement, and toxic reactions, conditions which might be questioned as being tolerated. The MTD, often estimated from toxicity observed after exposure for 6–8 weeks, was quite inaccurate. The high dose levels had to be adjusted downwards in many documented studies before the study was completed because many treated animals died from effects not related to oncogenicity. In other cases, doses were adjusted upwards due to lack of an observable toxic effect. Due to the importance in determining accurate doses for long-term bioassays, the Agency requires conducting adequate preliminary toxicity range-finding studies, with a minimum of 90 days exposure.

Information on chemical tissue disposition (including absorption, disposition, metabolism, and excretion), might provide data which would help establish more precise dose levels from 90 day preliminary range-finding studies. Such data often are not available due to the expense of obtaining them. An alternative is to allow for adjusting the dose levels as the study proceeds in order to achieve the highest tolerated dose. While such adjustments present difficulties in data analysis and extrapolation, they may be necessary in some cases, to achieve the desired performance standards for the High Dose Level.

Lower Dose Levels: Two lower dose levels are proposed, fractions of the high dose level ranging down to no less than 10% of the high dose level. While a well selected single dose might be adequate to assess for oncogenic potential, the two additional dose levels provide: (a) assurance of an adequate study in the event of unpredicted toxicity occuring at the High Dose, (b) some information regarding the dose-response relationship, and (c) additional data which can be used in statistical evaluation of an oncogenic response.

The Agency has considered several other alternatives including (a) two dose levels (HDL and ½ HDL), (b) four doses (HDL, two middle dose levels, and a low dose approximately 1/100th of the High Dose), and (c) a process in which the number and range of doses is not defined but rather a requirement that data be developed sufficient for the Agency to conduct a risk assessment including dose-response analysis. Under alternative (c), a well-conducted study with two dose levels, such as in alternative (a) might provide sufficient data for an initial assessment of oncogenic potential. Should a positive result be obtained, however, additional studies, including more dose levels, might be necessary to provide adequate data necessary to make a scientific risk assessment. A serious disadvantage, that of delayed availability of results, might occur with option (c). An EPA review of many studies by the National Cancer Institute using two dose levels, MTD and ½ MTD, revealed that in many cases the greatest oncogenic response was achieved at the ½ MTD level. Conceivably, a higher oncogenic response might also have occurred had a third lower dose been included in those studies. Decrease survival of the animals at the MTD level may often account for this phenomenon; however, other mechanisms, e.g., competition between cell killing and cellular transformation, and altered metabolism may be determination of this inverse relationship. The EPA thinks that the proposed three dose levels, provide a reasonable balance between scientific needs and cost.

For Non-Oncogenic Chronic Effects Test Standards: The experiment is to be designed to allow for a dose-response analysis and "no observed effect." The highest dose, however, must be moderately toxic with lethality evident. The basis for these standards is the belief that a threshold may exist for most non-oncogenic effects and can be used in predicting risk at low exposure levels. The Agency is not proposing a specific number of dose levels required to meet these performance standards although it is expected that 3–4 may be needed to comply with the proposed standards.

For the Combined Chronic Effects Test Standards: The number of dose levels may vary with the species. For the mouse, three dose levels are proposed as it is intended to provide primarily oncogencity data and thus the dose used in the oncogenic effects test are sufficient. It could, of course, also provide valuable information on other chronic effects. For the non-rodent, criteria established for the Non-Oncogenic Chronic Effects Test Standards are to be followed. The rat is to provide data for both oncogenic and other chronic effects and thus dose levels meeting the requirements for both the Oncogenic and Non-Oncogenic Chronic Effects Test Standards must be selected. The combined Chronic Effects Test Standards should provide a sensitive test for both oncogenicity and chronic toxicity.

Clinical Procedures

The loss due to cannibalism or autolysis is largely preventable by careful and frequent clinical observations to detect weak or dead animals. Impending morbidity and mortality is often not evident a full day in advance, especially with rodents. The Agency therefore proposes observation of animals every 12 hours or more frequently to assure that no more than 5% of the animals in any group are lost from the experiment due to autolysis, cannibalism, missing from cage, etc. This is considered achievable through the use of proper operating practices and careful, clinical examinations.

Clinical data may also be used to predict onset and development of toxic effects at an early stage and help in antemorten and necropsy diagnosis. The three standards vary in the extent of proposed clinical tests. Only routine hemotology is proposed for the Oncogenic Effects Test Standards. In addition to hemotology, blood chemistry, urinalysis, and functional capacity studies are also proposed in the Non-Oncogenic Chronic Effects Test and the Combined Chronic Effects Test Standards for a subset of rat groups (8/group) and for all non-rodents. The reasons for the differences in proposed clinical tests are as follows: Hematology data can be used to predict the development or aid in the diagnosis of leukemia and other hematopoietic disorders of relevance to an assessment of oncogenic potential. However, other tests, such an urinalysis, have relatively little value in the oncogenicity test, except perhaps to detect other aspects of toxic effects. In contrast, results of

hemotology and biochemical tests have considerable value in the determination of the extent or profile of other chronic toxic manifestations, especially as related to clinical and pathological observations.

Pathology Examination

It is crucial to the successful conduct of the study that an adequate pathology examination be planned for and accomplished with quality control procedures implemented at all steps in the study. For this reason the Agency proposes stringent requirements in regard to the qualifications of the responsible pathologist and in the thoroughness with which gross and microscopic examinations are conducted. Diagnosis can only be provided for those lesions presented on the microscopic slide. Even the most careful microscopic evaluation is of no value when lesions are lost due to autolysed tissues, an inadequate gross necropsy, or failure to recognize and select lesions at necropsy, blocking or slide preparation. While there is little controversy regarding the need for a careful and thorough gross necropsy considerable disagreement exists as to the extent of microscopic examination that is needed for a routine evaluation for oncogenicity.

There are differences of opinion among pathologists regarding the number of animals and tissues from each animal that should routinely be examined microscopically. Most frequently recommended have been the following:

(1) All tissues in the highest dose and control groups with the extent of subsequent pathology in the intermediate dose levels depending on the types and significance of the high dose level findings, e.g., examinations of gross lesions and tissues found to have tumors in the high dose group (target tissues).

(2) A small group (6–8) of selected tissues per animal;

(3) Random sampling a percentage of animals in the test, e.g., ten percent of each group.

(4) Major tissues from all animals.

The Agency has chosen the 4th approach. The Oncogenic Effects Test Standards propose microscopic examination of approximately 30 different organs or tissues of each animal, a few with multiple sections. This represents about 40,000 tissue sections per chemical tested and entails over three-quarters workyear effort by a diagnostic pathologist.

The proposed microscopic examination of all animals in the oncogenic test standards is based upon the knowledge that: (a) oncogenic response occasionally occurs in the lower dose groups while not in the high dose group, (b) dose-related variations may occur in the target organs or degree of metastasis, and (c) there is greater likelihood of missing rare tumors or those occuring in small incidence if only a single group is microscopically examined. There can be little doubt that a very thorough examination may be needed to detect early and/or small lesions, those in small organs, and those that resulted from metastasis and are in a minute form.

For chronic effects other than oncogenicity, dose-response relationships and a no-effect-level are to be determined. This will necessitate an even greater degree of pathology examination for all animals in the Non-Oncogenic Effects and the Combined Chronic Effects Test Standards. In addition to those tissues designated in the Oncogenic Effects Test Standards, several other tissues or multiple sections of certain organs are also proposed for examination in the Non-Oncogenic Effects and the Combined Chronic Effects Test Standards.

The Agency has not specified that pathology diagnoses be in accordance with any specific classification or nomenclature system. Various systems, e.g., SNOP (Systematized Nomenclature of Pathology, The College of American Pathologists), a modified-version of SNOP, the World Health Organization's International Histological Classification of Tumors, and that being used by the National Center for Toxicological Research, are being considered. The use of a uniform classification and reporting system would greatly facilitate the Agency's review and evaluation process. Such a system may be proposed at a future date along with data formatting requirements.

In order to achieve consistancy in diagnosis and prevent biassed diagnoses, it is desirable that the same pathologist examine all tissues of all animals in the test. The Agency realizes that this might not be practical or possible in all cases, especially for the Combined Chronic Effects Test and thus proposes that the same pathologist examine all tissues of one species. Another alternative being considered is to require the same pathologist to examine tissues from one sex of one species. This latter alternative would allow for more pathologists to be assigned to the study and facilitate completion of the examination. Viewpoints as to how best to achieve the desired quality control and prevention of bias in the pathology examination under practical conditions are solicited.

Routine weighing of organs is not proposed in the Oncogenic Effects Test Standards as the data are not considered of sufficient value in the assessment of oncogenic potential. However, organ to body weight ratios are of value in assessing chronic toxicity and thus weighing of a few major organs is proposed in the Non-Oncogenic Chronic Effects Test Standards and in the Combined Chronic Effects Standards.

Additional Scientific Studies

Other data might be valuable in relating animal toxicological findings to man, selecting appropriate test species, and determining chronic dose levels, e.g., that pertaining to metabolism, pharmacokinetics, and enzymology. Obtaining such data is often expensive, and the appropriate studies must be selected or designed specifically for the chemical to be tested. The Agency therefore proposes that the decisions as to the need for and extent of these additional studies (data needs) are usually best left to the discretion of the Sponsor. In some cases, however, they may be identified by the Agency and will be required in specific test rules.

Any animal metabolism and pharmacokinetics data provided by the Sponsor will be considered by the Agency in the risk assessment process. Because more accurate risk assessments may be made from comparative data, known data on human metabolism and pharmacokinetics (often available only from accidental or workplace exposures or in the scientific literature), might also be requested either informally or by a Section 8(d) rule.

Request for Comments on Proposed Test Standards

In the previous sections, the proposed standards have been discussed along with other alternatives considered. The public is invited to submit viewpoints and supporting data on any and all aspects of the standards and supporting documentation. Comments on the following issues are of particular interest to the Agency:

(a) Qualifications of professional personnel conducting tests

(b) Specifications for diet and chemical analyses

(c) Choice of animal species, e.g., rodents and non-rodent (dog) failure to designate specific strains requirements for controls

(d) Starting exposure as weanlings rather than in utero or as newborn animals

(e) Use of a set number of animals per groups, e.g., fifty, versus number based upon a specified sensitivity, e.g. increase of 10% in tumor rate

(f) Duration of exposure and observation periods

(g) Determination of doses and dose levels.

(h) Extent and methods of conducting clinical and pathology examinations.

(j) Reporting requirements.

IV. Policy Considerations

Relationship to EPA Pesticide Registration Guidelines

EPA's Office of Pesticide Programs has proposed testing guidelines under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended (FIFRA) (86 Stat. 973; 89 Stat. 751; 7 U.S.C. 136 et seq.) which contain data requirements comparable to those proposed by these standards (43 FR 37336, August 22, 1978).

In addition, EPA or other Federal agencies and departments may issue regulations under other statutory authorities which would impose requirements similar to those in these standards. The Agency's policy is to reduce the burden on the regulated public which might arise from conflicting requirements under these different sets of regulations and guidelines. Therefore, although the proposed TSCA and proposed FIFRA test standards differ in some significant ways because of updated OTS views, the final TSCA test standards and final FIFRA guidelines will be consistent to the extent permitted by the different laws. Among major differences are: the use of a non-rodent in the non-oncogenic chronic and combined chronic standards, the duration of exposure, and the qualifications of key scientific personnel. A list comparing the diferences in the two standards appears in the Support Document.

Comments received in response to the FIFRA proposed guidelines will be reviewed along with those received from this proposal in arriving at final standards for both FIFRA and TSCA.

Relationship to Interagency and International Test Guidelines

The final TSCA standards also will be as consistent as possible with FDA's Good Laboratory Practice regulations and other data or testing requirements established by U.S. Federal regulatory bodies. EPA has joined with the Food and Drug Administration (DHEW) the Consumer Product Safety Commission (CPSC), and the Occupational Safety and Health Administration (DOL), and the U.S. Department of Agriculture (USDA), to form the Interagency Regulatory Liaison Group (IRLG). The general purpose of the IRLG is to coordinate the regulatory activities of the four agencies, and one IRLG committee is developing testing protocols for human health and environmental effects which would be acceptable to all four agencies. EPA will review the proposed IRLG guidelines when they are available and revise its test standards as appropriate.

In developing these and other areas under TSCA, the United States has been a full and regular partner in extensive international consultations and activities, especially through the Organization for Economic Cooperation and Development (OECD). The United States is the lead country for the projects on Long-Term Toxicology and Good Laboratory Practices. The preparation of test guidelines by the World Health Organization is also being followed closely. The Agency places high priority on these international activities and will attempt to achieve an international harmonization of standards and regulatory approaches in an attempt to eliminate trade and regulatory barriers, ensure that the international chemical industry is not hampered unnecessarily by vaque or inconsistent requirements and that data developed in one country are acceptable in another.

Although TSCA sets forth specific requirements and deadlines, it provides room for some discretion and flexibility. To the extent possible, EPA is attempting to make our regulatory approaches consistent with those of other countries and international organizations.

Comments from other countries and international organizations will be solicited and given serious consideration as the Agency further develops regulations. Agreements reached through the international activities in which the United States Environmental Protection Agency is engaged will be reflected in EPA's national regulations, in accordance with rulemaking requirements.

Specificity of Details in Standards

The Agency must assure that sufficient data are developed and in a manner and quality so that a hazard identification and risk assessment can be performed. It is recognized that many toxicology laboratories have the scientific staff and facilities to conduct the necessary tests in a highly professional manner, and that in those cases, only general guidance as to the type of data might suffice. In many well-documented cases, however, inadequate data have been provided to EPA or other agencies. For this reason, standards are detailed enough to provide for the most essential elements for development of reliable data. See discussion in the preamble to the Good Laboratory Practices, also apearing in today's **Federal Register**. The Agency has decided not to propose even more detailed requirements at this time, although other aspects have been suggested to the Agency and are under consideration. As these standards are of a generic nature, more specific requirements, related to the chemical substance(s) to be tested, may be proposed in specific chemical test rules.

Future Health Effects Test Standards

Standards for tests such as acute/subchronic toxicity, teratogenicity, and other health effects, will be proposed later this year for use in Section 4 test rules for these effects.

The Agency is also considering proposing certain biological screening tests to identify chemicals that may present a potential chronic health risk. Although short-term tests utilizing both mammalian and sub-mammalian species can be applied in the initial evaluation of the biologic activity of certain chemical substances, EPA does not believe that any short-term test or test battery is sufficiently validated at this time to replace long-term bioassays. EPA is, however, undertaking various activities to validate such short-term tests, and will consider proposing such standards upon their validation.

V. General Provisions

Elsewhere in this preamble, the Agency has explained that the standards proposed today are intended for use in future chronic effects test rules, and that the Agency will propose test rules for other health and environmental effects beginning later this year. Because today's proposal thus initiates the Agency's long-term program for testing chemicals through TSCA test rules, the Agency also proposes establishing a Part that provides information, test standards, and other general regulatory criteria applicable not only to the planned chronic effects test rules, but also to other future health and environmental effects test rules as well. These general provisions are reviewed below and proposed as new Part 770.

Information and Definitions

Sections 770.1, 770.2 and 770.3 would provide generally applicable informational provisions based primarily on the legal criteria summarized in Section I of this preamble. These provisions would describe the general structure of TSCA test rules, explain the purpose of these rules as a means of developing data for risk assessment purposes, summarize the legal authority for test rules, identify the persons responsible for developing test data and submitting these data to EPA, and provide generally applicable definitions Because these are intended as general provisions, the Agency would supplement these provisions by proposing other provisions specific to particular chemicals or specific to particular test standards, as necessary and appropriate.

Many of the definitions proposed for Section 4 test rules are identical to definitions finalized or proposed for regulations under Sections 5, 6, and 8 of TSCA. In addition, the Agency proposes new definitions or revised versions of existing definitions to meet the specific purposes of TSCA test rules.

Confidentiality and Public Access to Information

Section 770.4 of those regulations would establish general procedures for handling information claimed as confidential. In addition, specific procedures for handling confidentiality claims related to chemical identity will be proposed, if necessary, when the Agency applies these test standards to specific chemical substances or mixtures.

When information submitted is covered by a claim of confidentiality asserted in accordance with these rules, EPA will disclose that information only to the extent permitted by the Act, these rules, and EPA's Public Information rules, 40 CFR Part 2. Basically, this means that EPA will not disclose information claimed as confidential without prior notice to the submitter. If a person asserts a claim but fails to submit a sanitized copy or the required substantiations, he will be given an opportunity to correct this problem before EPA releases the information.

EPA will review all confidentiality claims asserted for information included in reports submitted to meet test rule requirements. In accordance with Section 14(b) of the Act, EPA will grant confidentiality for such information only if the Agency determines that release would disclose confidential information concerning the manufacturing or processing process for a chemical substance or mixture, or the confidential proportions of a mixture.

As discussed in the Support Document, EPA would require submission of a second sanitized copy of a health and safety study if a person asserts a claim of confidentiality for any information contained in the health and safety study, and substantiation of a claim of confidentiality at the time of submitting the information. First, for this type of information Congress intended public disclosure of the data to the extent possible. Second, because EPA expects a high volume of requests for disclosure, EPA must have the substantiation readily available in order to reduce the administrative burden of responding to Freedon of Information Act requests. And third, EPA must be prepared to respond to these requests speedily. Finally, the substantiations burden is further justified by the need to discourage ill-founded claims. Substantiation aids the submitter in understanting the findings which are required by law to support confidentiality claims. Experience with the Inventory reporting regulations indicates that detailed substantiation requirements significantly reduced the number of claims. This should result in a higher level of public information and a reduced burden on EPA to evaluate and protect information erroneously claimed to be confidential.

To satisfy this substantiation requirement, a person must provide written answers to a series of questions developed by EPA. The basis for this requirement, and the draft substantiation questions, are included in the Support Document.

Compliance and Enforcement

Section 770.5 proposes general standards for assessing the validity of data submitted under TSCA test rules. In the first instance, the Agency would review these data in terms of the test standards and other requirements in a test rule. Because data submissions that contain data that is intentionally false or misleading, or that omit required data cannot conform to the testing and reporting standards in a rule, the data would be presumed to be invalid. As a result, the Sponsor would be in violation of the test rule requirement that data be developed and submitted in accordance with the test standards. Further, data submissions that include such invalid data would also be in violation of the requirement that data developed in accordance with the test standards be submitted to the Agency by the deadline given in the rule. Similarly, where a testing facility refuses entry to EPA inspectors, any data submitted from such a facility would be considered to be invalid, and subject to the same consequences.

If data do not meet the requirements of the testing rule, including standards, the Agency may impose penalities for violation of the test rule, or require the test Sponsor to submit additional data as required by the test rule under an extended deadline, or otherwise use the regulatory and penalty provision of TSCA to enforce the test rule requirements. While the Agency would first review data submitted under a TSCA test rule to determine if it meets test rule requirements, the Agency is not precluded from considering non-confirming data for risk assessment purposes.

The Agency considers the success of the testing program to be vital to the effectiveness of the TSCA chemical control program as a whole. Consequently, every effort to insure compliance with the mandates of Section 4 in all rules and standards promulgated thereunder will be made. In this regard, the Agency intends to assure that standards regarding the development of test data are complied with by doing periodic inspections of facilities conducting tests required by Section 4 rules. However, the Agency intends to take a reasonable approach towards enforcing against minor deviations and technical violations.

The Agency has authority to proceed against responsible corporate officials under Sections 15 and 16 of TSCA since they are "persons" within the meaning of these sections. The Agency is also exploring the boundaries of the liability of independent testing facilities for violations of any Section 4 rules.

Revision and Modifications of Test Standards

Section 770.6 would provide general standards relating to the revision and modification of test standards. The Agency intends these standards to be dynamic and will provide for the periodic review of the scientific basis of the standards. Thus in accordance with Section 4(b)(2)(B) of the Act, the Agency will review the adequacy of all codified, generic test standards not less than once every 12 months after the standards are first incorporated into a test rule and will institute proceedings to revise the standards, if necessary. The Agency will revise the standards in accordance with the provisions of the Administrative Procedure Act (5 U.S.C. 551 et seq.). Changes to the standards which have significant impact would require notice

and opportunity for comment, but routine or minor changes may be made without proposal when the Agency determines such to be impractical and unnecessary.

Although EPA plans generally to incorporate generic test standards into test rules, the Agency also recognizes that generic standards may not be suitable for every chemical proposed for such testing. For example, test standards relating to the route of administration and the form of the chemical to be tested would necessarily be specific for each chemical and would be proposed at the time that the Agency identifies particular chemicals for testing. For this reason, requirements relating to standards of this kind are not included in the present proposal.

In addition, in some cases, the Agency may find that the generic standards are not completely suitable for a particular chemical and that a modification of the standards for that chemical is indicated. For example, the metabolic characteristics of a particular chemical may indicate that rodents are inappropriate as the test species, that a different dosing regimen is appropriate, or that tissues other than those specified in the generic test standards should be microscopically examined. In such cases, the Agency would propose chemical-specific modifications of the generic test standards.

VI. Economic Analysis

A regulatory analysis is not required with respect to these proposed test standards because the standards themselves do not impose any costs on any person at this time. The Agency recognizes, however, that long-term health effects testing is expensive and time-consuming. The estimated cost per chemical for the test standards proposed in this notice (based upon feeding studies) is approximately as follows:

Oncogenic effects	$400,000
Non-oncogenic chronic effects	$550,000
Combined oncogenic and non-oncogenic chronic effects	$800,000

The cost of prechronic range-finding studies is approximately as follows: oncogenic—$50,000; non-oncogenic chronic—$100,000; combined chronic—$130,000. Where these studies have not been previously conducted, the cost for the test standards will be increased by these amounts.

The use of point estimates unfortunately gives an impression of preciseness which is not intended. Actual costs of long-term testing will vary substantially (perhaps 10–40%), depending on a number of factors, including, for example, the chemical tested, laboratory performing the test, number of dose levels, species, route(s) of exposure, extent of pathology conducted, duration of tests, and inclusion of ancillary studies.

Many chemicals that will be subject to Section 4 rules may not require these specific chronic effects tests. Rather, these standards are being developed as part of an array of standards to be required selectively and as needed. Furthermore, no chemical will have to undergo all three tests. Depending on the data already available and the additional data needed to assess risks, a chemical could be required to undergo either oncogenicity or non-oncogenic chronic toxicity testing or both. Where both are required, testing can be performed in accordance with the combined test standard, thus allowing a saving of approximately $150,000 compared to the cost of separate testing for oncogenic and non-oncogenic effects.

Changes in cost per chemical could be achieved by modifications in the requirements set forth in the testing standards, e.g., reducing or increasing the number of dose levels, the number of tissues to be examined by the pathologists, the use of less highly skilled individuals, or performing testing in a non-rodent species. EPA believes that the proposed standards are necessary to assure that data developed through test rules are adequate for their intended use in risk assessment, and that abbreviated standards generally could result in a significant reduction in the quality and reliability of the resulting data and could preclude adequate assessment of hazard potential. For example, data derived from the NCI bioassay program, which utilizes two dose levels, rather than the three proposed levels, may adequately assess potential for oncogenicity but the data have serious limitations as pertains to assessing dose-response relationships.

EPA's issuance of testing rules (requiring testing of specific chemicals in accordance with the testing standards) will, of course, impose costs on persons required to undertake the testing. Which chemicals and how many chemicals will be required to undergo such testing remain to be decided. Given this, it is difficult to estimate the potential total cost of these standards, as incorporated into rules requiring testing of particular chemicals. Assuming that approximately 15 to 30 chemicals a year will be tested under Section 4 test rules using these particular test standards, their total annual cost is estimated to be $6 to $27 million.

The proposed standards could apply to both existing and new chemicals within any chemical category for which testing rules are issued. Thus, testing requirements may have some impact on development of new chemicals within categories selected for testing. The Agency recognizes that there is some potential for impact on innovation in the chemicals industry and that the extent of this impact will depend on the way in which the Agency selects and defines testing requirements for new chemicals.

VII. Public Participation

During the development of these proposed standards, numerous meetings and discussions were held with non-EPA scientists and with an Agency Work Group consisting of Agency scientists, other EPA officials and scientists from other Federal Agencies. At meetings on July 25 and August 15, 1978, scientists from industry, environmental groups and EPA, reviewed preliminary drafts, discussed the Agency's basic approach to developing the standards, and considered scientific alternatives for various aspects of the standards (43 FR 34841, August 7, 1978).

Drafts of these proposed standards were also discussed with the EPA's Science Advisory Board at public meetings held on June 22 and August 18, 1978 (43 FR 23013, May 30, 1978; 43 FR 32185, July 25, 1978). The Science Advisory Board also solicited public comments on the proposed standards at those meetings.

In addition to these workgroup and public meetings, other meetings on specific scientific issues were held. One, on pathology requirements, was held on April 3, 1978. On August 10, 1978, a workshop was held between Agency and National Cancer Institute scientists to discuss statistical and pathological aspects of oncogenicity and chronic toxicity bioassays.

This public participation has significant influenced the development of these proposed standards and associated provisions.

Note.—Comments previously presented to the Agency in response to the proposed Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Guidelines for the Registration of Pesticides (43 FR 37336, August 22, 1978), are available to the Office of Toxic Substances and will be considered along the comments to this proposal in finalizing the TSCA standards. Previous submitters to the FIFRA proposal may supplement their earlier comments.

VIII. Public Meetings

EPA will hold public meetings during the comment period to provide the

public an opportunity to present comments and questions on these proposed standards. The purpose of these meetings is to enable interested persons to provide oral comments on the proposed rulemaking to EPA officials who are directly responsible for developing the standards and supporting provisions of the rule. The public meetings will start with a short summary by EPA of the proposed standards to be followed by oral presentations from the floor of no more than 10 minutes per person, company, or organization, depending upon the number of requests. EPA will allot speaking times on a first-come basis, although the Agency reserves the right to alter the order depending upon the nature of the particular comments and other relevant factors. If time permits, following these prepared presentations, EPA will receive any other comments from the floor.

These meetings will be held during the week of July 9 in Chicago and during the week of July 16 in Washington, D.C. Further information on these meetings will be published in the **Federal Register.**

Persons who wish to present their comments at any one of the meetings should contact EPA no later than four days before the meeting date by calling toll-free at 800–424–9065 (in Washington, D.C., call 554–1404), or by writing to the address listed at the beginning of this preamble under "For Further Information Contact."

Presenters are urged, but not required, to submit copies of their statements on the day of the meeting. All such written materials will become a part of EPA's record for this rulemaking. In addition, the Agency will transcribe each meeting and will include the written transcripts in the public record.

IX. Public Record

EPA has established a public record for this rulemaking (docket number OTS 046003) which is available for inspection in the OTS Reading Room from 9:00 a.m. to 5:00 p.m. on working days (Room 710E, 401 M Street SW., Washington, D.C. 20460.) This record includes basic information considered by the Agency in developing this proposal. The Agency will supplement the record with additional information as it is received. The record includes the following categories of information:

(1) USEPA–OTS. "Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules".

(2) USEPA–OTS. "Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules": Support Document.

(3) Working drafts of the proposed rules, the preamble, and the Support Document which were available for public comment.

(4) Correspondence pertaining to development of the standards, preamble, and support document. (This does not include inter- or intra-agency correspondence, unless specifically noted in the index of the rulemaking record).

(5) Minutes, summaries, or transcripts relating to public meetings held to develop the standards.

Published documents cited in this preamble are incorporated in the record by reference. EPA will accept additional material for the record at any time between this proposal and the final designation of the rulemaking record. EPA will identify the complete rulemaking record on or before the date of promulgation of these requirements, as prescribed by TSCA Section 19(a)(3). The record of this proceeding is available in the OTS Reading Room.

Note.—Under Executive Order 12044, EPA is required to judge whether a regulation is "significant" and therefore subject to the procedural requirements of the Order or whether it may follow other specialized development procedures. EPA labels these other regulations "specialized". I have reviewed this regulation and determined that it is a specialized regulation not subject to the procedural requirements of Executive Order 12044.

Dated: April 27, 1979.

Douglas M. Costle,

Administrator.

It is proposed that new Parts 770, 771 and 772 be added to Chapter I of Title 40 as follows:

PART 770—TEST RULES FOR CHEMICAL SUBSTANCES AND MIXTURES

General

Sec.

770.1 Scope, purpose and authority.
770.2 Definitions.
770.3 Applicability.
770.4 Confidentiality and public access to information.
770.5 Compliance.
770.6 Revisions and modifications of test standards.

PART 771—IDENTIFICATION OF CHEMICAL SUBSTANCES AND MIXTURES TO BE TESTED [RESERVED]

PART 772—STANDARDS FOR DEVELOPMENT OF TEST DATA

Subpart A—General [Reserved]

Subpart B—Good Laboratory Practice Standards [Reserved] [1]

Sec.

772.110–1 Good Laboratory Practice Standards for Health Effects [Reserved] [1]

Subpart C—Acute and Subchronic Health Effects [Reserved]

Subpart D—Chronic Health Effects

Sec.

772.113–1 General
772.113–2 Oncogenic Effects Test Standards
772.113–3 Non-Oncogenic Chronic Effects Test Standards
772.113–4 Combined Chronic Effects Test Standards

Subpart E—Mutagenicity [Reserved]

Subpart F—Teratogenicity/Reproductive Effects [Reserved]

Subpart G—Short-Term Tests for Health Effects [Reserved]

Subpart H—Behavioral/Neurotoxicity Health Effects [Reserved]

Subpart I—Other Health Effects [Reserved]

Subpart J—Epidemiological Studies [Reserved]

Subpart K—[Reserved]

Subpart L—Physical and Chemical Properties [Reserved]

Subpart M–Chemical Fate [Reserved]

Subpart N—Ecological Effects [Reserved]

Subparts O–Z—[Reserved]

Authority: Section 4, Toxic Substances Control Act (TSCA) (90 Stat. 2006; 15 U.S.C. 2603).

PART 770—TEST RULES FOR CHEMICAL SUBSTANCES AND MIXTURES

General

Sec.

770.1 Scope, purpose and authority.
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Authority: Section 4, Toxic Substances Control Act (TSCA) (90 Stat. 2006; 15 U.S.C. 2603.)

General

§ 770.1 Scope, purpose, and authority.

(a) *Scope.* As authorized by Section 4 of the Toxic Substances Control Act (the

[1] See FR Doc 79– also in this Part II of the **Federal Register.**

"Act"), Part 771 of this Chapter provides test rules that require manufacturers (including importers) and processors of chemical substances and mixtures ("chemicals") to develop test data in accordance with the rule and submit this data to the Environmental Protection Agency ("EPA"). Part 771 identifies the chemical substances and mixtures for which data are to be developed, provides deadlines for the submission of data to EPA, and prescribes test standards for the development of the data by reference to the standards in Part 772 and specific modifications thereto. Part 772 includes standards relating to the design and conduct of tests, and the analysis and reporting of test data.

(b) *Purpose.* Each TSCA test rule is designed to require manufacturers and processors of the chemicals identified in the rule to develop data on the health and/or environmental effects of these chemicals so that the Administrator will have the data that are necessary to determine whether or not the tested chemicals present a risk of injury to human health or the environment. When data developed in accordance with the rule (and any other relevant information) indicate to the Administrator that regulatory action may be appropriate, the Administrator will use the data developed through the rule (and any other relevant information) to make decisions and support regulatory actions in accordance with the provisions of Section 5, 6, 7 and 9 of the Act.

(c) *Authority.* Section 4 of the Act authorizes the Administrator to promulgate rules for development of test data on chemical substances and mixtures, and specifies that each test rule must, among other things, identify the chemicals to be tested and provide standards for development of test data. The Act further specifies that each test rule must include standards that prescribe the health and environmental effects for which information is to be developed, the data that are to be developed, the analyses to be done on the data, and, if necessary to assure reliable and adequate data, test methodology and other requirements. In order to require that a chemical be tested in accordance with EPA test standards, the Administrator must make three findings relating to the chemical's risk potential and the insufficiency of data then available to EPA.

(1) First, the Administrator must find either that the manufacture, distribution in commerce, processing, use, disposal, or some combination of these activities involving the chemical may present an unreasonable risk of injury to health or the environment, or that the chemical is or will be produced in substantial quantities and that there is or may be significant or substantial human or environmental exposure to the chemical (Sections 4(a)(1) (A)(i) and (B)(i) of the Act).

(2) Second, the Administrator must find that existing data and experience relating to the chemical are insufficient to reasonably determine or predict the effects on health or the environment of the manufacture, distribution in commerce, processing, use, or disposal of the chemical or of any combination of these activities (Sections 4(a)(1) (A)(ii) and (B)(ii) of the Act.)

(3) The third finding of that testing is necessary to develop the requisite data (Sections 4(a)(1) (A)(iii) and (B)(iii) of the Act).

§ 770.2 Definitions.

(a) For the purposes of Parts 770, 771, and 772, the following terms shall have the meaning contained in Section 3 of the Toxic Substances Control Act, 15 U.S.C. 2601 *et seq.*, and any regulation issued under that Act: "Administrator"; "By-Product"; "Chemical Substance"; "Commerce"; "Co-Product"; "Distribute in commerce" and "Distribution in commerce"; "Health and Safety Study"; "Intermediate"; "Manufacture"; "Manufacture for commercial purposes"; "Possession or control"; "Process"; "Process for commercial purposes"; and "Standards for development of test data."

(b) For the purposes of Parts 770, 771, and 772, the following terms shall have the meaning contained in the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321 *et seq.*, and the regulations issued under that Act: "cosmetic," "device," "drug," "food," and "food additive." In addition, the term "food" includes poultry and poultry products, as defined in the Poultry Products Inspection Act, 21 U.S.C. 453 *et seq.*; and eggs and egg products, as defined in the Egg Products Inspection Act, 21 U.S.C. 1033, *et seq.* "Pesticide" shall have the meaning contained in the Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. 136 *et seq.*, and the regulations issued thereunder.

"Act" means the Toxic Substances Control Act, 15 U.S.C. 2601 *et seq.*

"Control substance" means any chemical substance or mixture or other material that is administered to the test system in the course of a study for the purpose of establishing a basis for comparison with the test substance.

"EPA" means the U.S. Environmental Protection Agency.

"Importer" means any person who imports a chemical substance, including a chemical substance as a part of a mixture or article, into the Customs Territory of the United States, and includes the person primarily liable for the payment of any duties on the merchandise or an authorized agent acting on his behalf. Importer also includes, as appropriate:

(1) The consignee;

(2) The importer of record;

(3) The actual owner, if an actual owner's declaration and superseding bond has been filed, in accordance with CFR 141.20; or,

(4) The transferree, if the right to draw merchandise in a bonded warehouse has been transferred in accordance with Subpart C of 19 CFR 144. For the purpose of this definition, the Customs Territory of the U.S. consists of the 50 States, Puerto Rico, and the District of Columbia.

"Impurity" means a chemical substance which is unintentionally present with another chemical substance or in a mixture.

"Person" means any natural person, firm, company, corporation, joint-venture, partnership, sole proprietorship, association, or any other business entity, any State or political subdivision thereof, any municipality, any interstate body and any department, agency, or instrumentality of the Federal Government.

"Processor" means any person who processes a chemical substance or mixture.

"Protocol" means a detailed description of the study design and conduct to be followed.

"Test data" means: (1) data, including chemical identity, from a formal or informal study, test, experiment, recorded observation, monitoring, or measurement; and (2) information concerning the objectives, experimental methods and materials, protocols, results, data analyses (including risk assessments), and conclusions from a study, test, experiment, recorded observation, monitoring, or measurement.

"Tester" means any person who develops health and/or environmental effects data to meet the requirements of a TSCA test rule, including any sponsor who develops such data and any independent consulting or contracting laboratory that develops such data.

"Test mixture" means a combination which results from mixing a test substance with another substance(s), including vehicle, dust-suppressant, feed, water, etc., for the purpose of

exposing the test system to the test substance.

"Sponsor" means any manufacturer (including importer) or processor of a chemical substance or mixture for which testing is required under a TSCA test rule who conducts and/or causes to be conducted health and environmental effects tests required by TSCA test rules and/or submits data developed in accordance with the rule to EPA. "Sponsor" includes any manufacture or processor who designates a second manufacturer or processor or a tester to develop such health and environmental effects data.

"Study Plan" means a work document prepared by the sponsor(s) or tester(s) which contains the proposed test protocol along with other pertinent information regarding the test to be conducted, including: the name and address of the sponsor and testing facilities including responsible administrative officers; identification of the substance to be tested; physical and chemical properties of the test substance; data on test substance stability under test and storage conditions; brief summaries of training and experience of each professional involved in the study, including the study director, toxicologist, veterinarian, pathologist(s) and pathology assistants; rationale for species/strain selection; summary of expected spontaneous chronic diseases (including tumors), genealogy, and life span of the strain and species of test animal selected; routes of exposure; description of diet to be used; rationale and supporting data for dose selection; proposed modifications and rationale for variance from applicable TSCA standards; and, schedule for initiation of studies greater than 90 days duration, including schedule for submission of interim progress and final reports to EPA.

"Test substance" means the specific form of a chemical substance or mixture that is used to develop data to meet the requirements of a TSCA test rule.

"Test system" means any animal, plant, microorganism, or subparts thereof to which the test or control substance is administered or added for study. "Test system" also includes appropriate groups or components of the system not treated with the test or control substance.

"Testing facility" means the persons, premises, and operational units that the tester uses or has used for the development of health and environmental effects data required by TSCA test rules.

§ 770.3 Applicability.

(a) Section 4(b)(3)(B) of the Act specifies that if the Administrator makes the Section 4(a) findings referenced in that section, the relevant test rules apply to each person who manufacturers or intends to manufacture, and/or to each person who processes or intends to process the chemical substances and mixtures for which test data are required. The section also provides that the Administrator may permit two or more of the manufacturers and/or processors who are required to conduct tests and submit data to the EPA to designate one such person or a qualified third person to conduct the tests and submit such data on behalf of the persons making the designation.

(b) Under Section 4(c) of the Act, any person required by a TSCA test rule to conduct tests and submit data may apply to the Administrator for an exemption from such requirement. If the Administrator determines that a chemical substance or mixture for which an exemption application was submitted is equivalent to a chemical substance or mixture for which data have been submitted to the Administrator pursuant to a TSCA test rule or are being developed pursuant to such a rule, and that submission of data by the applicant would be duplicative of data which have been submitted to the Administrator pursuant to a Section 4(a) rule or are being developed pursuant to such a rule, the Administrator must exempt the applicant from conducting tests and submitting data (Section 4(c)(2)). In accordance with procedures and rules authorized by Sections 4(c)(3) and 4(c)(4), those persons exempted from conducting testing and submitting data must be required to reimburse those persons submitting the data on which the exemption was based.

§ 770.4 Confidentiality and public access to information.

(a) A person may assert a claim of confidentiality for any information which he submits to EPA under Part 771.

(b) Any claim of confidentiality must accompany the information at the time it is submitted to EPA.

(1) If any information in a document is claimed as confidential, two copies of the document in which the information appears must be submitted.

(i) One copy of the document must be complete. In that copy, the submitter must clearly identify the data which are claimed confidential by marking the specific information on each page with a label such as "confidential business information," "proprietary," or "trade secret."

(ii) The second copy must be complete except that all information claimed as confidential in the first copy must be deleted. EPA will place the second copy in the public file.

(2) If the person does not provide the second copy, EPA will notify him of this fact by telephone or certified mail. If EPA does not receive the second copy within ten working days after the person receives this notice, the Agency will place the first copy in the public file.

(c) At the time a person submits the information to EPA, he must substantiate any claim of confidentiality for information contained in health and safety studies.

(1) If a person does not submit any substantiation, EPA will notify him of this fact by certified mail. If EPA does not receive the substantiation within ten working days after the person receives this notice, the Agency will place the information in the public file.

(d) EPA will disclose information that is covered by a claim of confidentiality asserted in accordance with this section only to the extent permitted by and in accordance with the procedures set forth in the Act, this section and Part 2 of this Title.

(e) If a person does not assert a claim of confidentiality for information at the time he submits it to EPA, the Agency may make the information public, including placement in the public file, without further notice to the person.

§ 770.5 Compliance.

(a) *General.* In order to satisfy the requirements of a TSCA test rule, the sponsor and/or other person who conducts or has conducted tests to meet the requirements in the test rule must test the chemical identified in the rule in accordance with the standards specified in the rule, including the appropriate good laboratory practice standards. The sponsor must submit test data and other required information to EPA on or before the data submission deadline specified in the rule.

(b) *Violations.* (1) Section 15(1) of the Act makes it unlawful for any person to fail or refuse to comply with any rule promulgated or order issued under Section 4. Section 15(3) makes it unlawful for any person to fail or refuse to (i) establish or maintain records, (ii) submit reports, notices, or other information, or (iii) permit access to or copying of records required by the Act or any rule promulgated thereunder. Thus, failure to comply with any aspect of a Section 4 rule or the submission of invalid data, as defined in Section 770.5(c), would be violations as defined by Section 15(1) and 15(3).

(2) Section 16(a) provides that any person who violates any provision of Section 15 shall be liable to the United States for a civil penalty of up to $25,000 per violation, with each day of violation constituting a separate violation. If a violation is knowing or willful, criminal penalties of up to one year in prison and $25,000 per day of violation may also be assessed under Section 16(b). In addition, under Section 17 of the Act, the Agency may take injunctive action to restrain persons from violating Section 4 rules and standards.

(c) *Invalid data.* Except as provided in Section 770.5(d), data submitted to satisfy a TSCA test rule may be presumed to be invalid if any of the following conditions is present:

(1) The test is not being or was not conducted in accordance with the data development standards in the rule. Non-conformity with any single standard is sufficient to invalidate a test; or

(2) The data submission to EPA includes information and data that is intentionally false or misleading, contains significant omissions, or otherwise does not fulfill the requirements of Section 4 or of a test rule promulgated pursuant to Section 4; or

(3) A sponsor and/or any person who is developing or has developed test data to meet the requirements of a TSCA test rule refuses to admit the Administrator or his delegate for the purpose of auditing test data or inspecting test facilities.

(d) *Non-conforming data submissions.* If a person submits data that was not developed or submitted in accordance with the test standards or other requirements in a rule, EPA may review the data and, if appropriate, use the non-conforming data in order to meet the purposes of the Act.

§ 770.6 Revisions and modifications of test standards.

(a) *Annual revision.* At least once each year, EPA will review the generic test standards to assess their suitability for development of the data required by TSCA test rules. If this review indicates that substantial revision is required, EPA will propose amendments to the standards in accordance with the rulemaking procedures of 5 U.S.C. 553. If this review indicates that minor changes are required, EPA will publish these changes in the **Federal Register** and notify persons currently subject to a test rule containing the standards by certified mail. In either case, EPA will review data developed in accordance with the standards in effect when the rule was promulgated.

(b) *Chemical-specific modification of test standards.* EPA may propose or review a test sponsor's proposal for chemical-specific modifications of test standards if the generic standards are not suitable for a particular chemical. In addition, EPA and the sponsor may agree to specify those details of test methodology that are not mandatory test standards.

PART 771—IDENTIFICATION OF CHEMICAL SUBSTANCES AND MIXTURES TO BE TESTED [RESERVED]

PART 772—STANDARDS FOR DEVELOPMENT OF TEST DATA

Subpart A—General [Reserved]

Subpart B—Good Laboratory Practice Standards [Reserved] [1]

Sec.

772.110–1 Good Laboratory Practice Standards for Health Effects [Reserved] [1]

Subpart C—Acute and Subchronic Health Effects [Reserved]

Subpart D—Chronic Health Effects

772.113–1 General.

(a) *Scope and purpose.*
(b) *Applicability.*
(c) *Definitions.*
(d) *Good laboratory practice standards for chronic health effects.*
(e) *Specific personnel requirements.*
(f) *Submission of study plan.*
(g) *Test or control substance concentration.*
(h) *Dietary requirements.*
(i) *Contaminant analysis of feeds and/or vehicles.*
(j) *Reporting requirements.*
(k) *Contents of final report.*

Subpart E—Mutagenicity [Reserved]

Subpart F—Teratogenicity/Reproductive Effects [Reserved]

Subpart G—Short-Term Tests for Health Effects [Reserved]

Subpart H—Behavioral/Neurotoxicity Health Effects [Reserved]

Subpart I—Other Health Effects [Reserved]

Subpart J—Epidemiological Studies [Reserved]

Subpart K—[Reserved]

Subpart L—Physical and Chemical Properties [Reserved]

Subpart M—Chemical Fate [Reserved]

Subpart N—Ecological Effects [Reserved]

Subparts O–Z—[Reserved]

Authority: Section 4, Toxic Substances Control Act (TSCA) (90 Stat. 2006; 15 U.S.C. 2603).

[1] See FR Doc. 79–14497 also in this Part II of the Federal Register.

Subpart D—Chronic Health Effects

§ 772.113–1 General.

(a) *Scope and purpose.* The standards in this subpart are designed to develop data on chronic health effects of chemical substances and mixtures ("chemicals") subject to chronic health effects test regulations under the Toxic Substances Control Act (TSCA) (P.L. 94–469, 90 Stat. 2003, 15 U.S.C. 2601 *et. seq.*). The EPA will use these data to assess the risk of chronic effects these chemicals may present to human health.

(b) *Applicability.* These standards apply to the development of chronic health effects data from the testing of chemicals specified in Part 771 of this subchapter.

(c) *Definitions.* The definitions in section 3 of the TSCA and the definitions in § 770.2 and § 772.110–1(a)(3), entitled "Good Laboratory Practice Standards for Health Effects," apply to Subpart D. In addition, the following definitions also apply to Subpart D.

(1) "Chronic health effects" means any differences between the control and test animals which may result from long-term chemical exposure and/or develop over a long latency period.

(2) "Oncogenic effects" means chronic health effects which result in benign and/or malignant neoplasms. These effects may be due to initiation and/or promotion mechanisms.

(3) "Test group" means a cohort of test animals which have been randomly selected and which are identical in species/strain, sex, age, source, husbandry conditions, and dose level.

(4) "Exposed group" means a test group, which is administered the test substance at a specific dose level.

(5) "Matched control group" means a test group, which does not receive the test substance but which otherwise is treated the same as the exposed group.

(6) "Test animal" means any animal in the study.

(7) "Exposed animal" means any test animal that receives or is exposed to the test substance.

(8) "Control animal" means any test animal that is not exposed to the test substance.

(d) *Good laboratory practice standards for chronic health effects.* The Good Laboratory Practice Standards for Health Effects in Section 772.110–1, Subpart B, apply to Subpart D.

(e) *Specific personnel requirements.* For the purposes of these test standards:

(1) There are two types of qualified pathologists:

(i) Board-Certified or Board-Eligible pathologist(s) who have a minimum of

three years of experience in pathology of the species of laboratory animals to be used; or

(ii) Other doctorate pathologists (D.V.M., M.D., Ph.D., D.D.S., D.O.) who have a minimum of three years of experience in gross, clinical, and/or histopathology of the species of laboratory animals to be used.

(2) A qualified veterinarian is one who is Board-Certified or eligible for certification by the American College of Laboratory Animal Medicine, and who has a minimum of two years of experience in laboratory animal science; and

(3) There are two types of qualified technical employees:

(i) One certified by the American Society of Clinical Pathology (HTASCP), or with equivalent training and experience.

(ii) One certified or eligible for certification by the American Association of Laboratory Animal Science (LTAALAS), or with equivalent training and experience.

(f) *Submission of study plan.* (1) The sponsor(s) of a study must submit a detailed study plan to the Agency at least 90 days before the study is initiated.

(2) The following information must be submitted:

(i) The name and address of the sponsor and testing facility including responsible administrative officials and project manager(s);

(ii) Brief summaries of the training and experience of each professional involved in the study, including Study Director, Veterinarian, Toxicologist(s), Pathologist(s) and Pathology Assistants;

(iii) Study protocol including rationale for species/strain selection, dose selection (and supporting data), route(s) of exposure, modifications or variance from applicable TSCA standards and rules;

(iv) Summary of expected spontaneous chronic diseases (including tumors), genealogy, and lifespan;

(v) Description of diet to be used and source of diet;

(vi) Data on test substance and stability under test and storage conditions;

(viii) Schedule for initiation and completion of major phases of long-term test(s); schedule for submission of interim progress and final reports to EPA.

(g) *Test or control substance concentration.* The tester must document that, at the time of administration, the test substance or mixture administered contains no less than 90 percent of the designated test substance concentration as specified in the sponsor-approved protocol. To accomplish this objective, the tester must conduct and document stability studies in accordance with Section 772.110–1, Subpart B, prior to initiation of a study and analyze the administered substance or mixture to determine:

(1) The rate of loss of the test substance by elution, degradation, or other means;

(2) The major degradation products, if any; and

(3) Analyze for initial concentration.

The initial mean concentration of the test substance must not vary more than ±5 percent from the designated concentration. To assure homogeneity in a test mixture, variability among randomly selected samples (at least 3) from the test mixture must not exceed ±10 percent from the means of the samples.

Note.—If a vehicle is needed in the preparation of the test mixture, either to dissolve, dilute or otherwise facilitate mixing or administering the test substance, the vehicle should be selected to have the following characteristics:

(1) It facilitates absorption but does not substantially alter the extent of distribution, metabolism, or retention of the test substance;

(2) It does not alter the chemical properities of the test substance or substantially enhance, reduce, or alter the toxic characteristics of the test substance;

(3) It does not substantially affect the food or water consumption or the nutritional status of the animals;

(4) It does not produce substantial physiological effects at the levels used in the study.

(h) *Dietary requirements.* (1) All rodents must be fed the standardized diet containing the nutrient levels and produced by feed stocks or ingredients as listed in Appendix A unless EPA approves another diet that the sponsor proposes as a substitute. The sponsor must request and obtain EPA approval at the time of study plan submission for diets for non-rodent species.

(2) The tester must not use feed 90 days after its manufacture. The tester must maintain as a part of the raw data a log showing the date each batch/lot of feed was manufactured and the last date it was administered.

(i) *Contaminant analysis of feeds and/or vehicles.* The sponsor must have each batch/lot of feed and vehicle analyzed to determine concentrations of contaminants listed in Appendix A of this section. The Agency considers this list to be minimal and not all inclusive. The Agency encourages the tester to conduct additional analysis for other contaminants that may affect the interpretation of the study results.

(j) *Reporting requirements.* The tester must submit to EPA all data generated by the test that is suggestive or predictive of the initiation and/or promotion of oncogenic or other chronic disease process(es) and all concomitant toxicologic manifestations. The tester must submit to EPA the following reports:

(1) "Study Plan" as required in § 772.113–1(f).

(2) "Interim Quarterly Summary Reports" outlining the current status of the study including any significant findings.

(3) "Final Test Report".

(k) *Contents of final test report.* (1) *Description of the test procedures.* (i) *Methodology.* Specification of test methods, including a full description of the study design and procedures, the length of the study, and the dates on which the study began and ended, must be stated.

(ii) *Deviation from standards.* The report must indicate all ways in which the test procedure deviated from test standards and must state the reasons for such deviations.

(iii) *Animal data.* Animal data must include:

(A) Species, strain and subline used, rationale for selection of species if it is different than that required in this subpart, and rationale for selection of strain and subline;

(B) Source of supply of the animals;

(C) Breeding Type—inbred, hybrid, outbred;

(D) Disease Control—specific pathogen-free, germ-free, conventional vaccinated;

(E) Description of any pre-test conditioning, including diet and quarantine;

(F) Initial number by sex, numbers of animals in each test group;

(G) Age and condition of each animal at beginning of study;

(H) Method of randomization used in assigning animals to each test group.

(iv) *Environmental conditions.* A description of the caging conditions must include number of animals per cage, bedding material, light (source and time cycle), diet (type and source), amount of diet (*ad libitum*, consumption), water source, amount of water, ambient temperature and humidity (range), cleaning agents used and any pest control materials.

(v) *Preparation of test mixture.* Data on preparation of test mixture must include: name of chemical(s), name of vehicle(s), preparation and calculations of concentrations, method(s) of

preparation, amount prepared each time, frequency of preparation, physical state, pH, stability and decomposition, storage, date(s) prepared and date(s) of final use.

(vi) *Dosing.* Dosing information must include:

(A) All dose levels administered;

(B) Method and frequency of administration;

(C) Duration of treatment;

(D) Total volume of material (i.e., test substances plus vehicle) contained in individual dosings;

(E) If the test substance is administerd in a vehicle, the method of randomization used in selecting samples of test mixture to assay for the test substance, the assay method used to determine the stability and homogeneity of the test substance being administered, and the results of this assay;

(F) For each dose level, the mean total amount of test substance administered per animal; and

(G) The rationale including discussion of alternatives for selection of the vehicle.

(VII) *Treatment for infectious diseases.* A description of the treatment(s) used to prevent or control infectious diseases if such treatment was undertaken during a test or shortly before a test was begun must include:

(A) For each individual affected animal: its identification number; the nature and severity of the disease; frequency of administration and name(s) of drug(s) or other treatment; total number of doses; total dose given, total time of treatment, the date of first observation and duration of disease; the date(s) of each treatment; and the outcome of the treatment(s) in relation to the disease and to the test results; and

(B) For each treatment: preparation administered, dose per administration (volume, weight, how measured); route of administration; site; and methods and instruments used.

(viii) *Methods of observation.* (A) A description of methods of observation;

(B) Checking individual animals;

(C) Weighing animals and if done on individual animals basis or by weighing of cages;

(D) Frequency of recording of observations;

(E) Frequency of measuring consumption of feed and water.

(ix) *Statistical procedures.* Appropriate statistical methods must be used to summarize test data, to express trends, and to evaluate the significance of differences in data from individual test groups. All data averages or means must be accompanied by standard deviations, to indicate the amount of variability in the raw data. In addition, the standard errors of the means may also be calculated, since they are useful in comparing means from different test groups; however, notations of statistically significant differences, accompanied by the confidence level or probability, may be used in place of the standard errors.

(x) *References:* Statistical and any other methods employed for analyzing the raw data; a list of references to any published literature used in developing the test protocol, performing the testing, making and interpreting observations, and compiling and evaluating the results.

(2) *Data reporting.* The test report must contain the following information, arranged and presented in the format specified.

(i) *For individual animals.* (A) *Significant time periods.* In tabular form, data must be provided showing, for each animal:

(*1*) Its identification number;

(*2*) Whether it was a scheduled kill, the method of kill, and, if so, whether it was moribund before being killed;

(*3*) Its age at the beginning of study, and date on which dosing was begun;

(*4*) The date, time of day, and the day of the study when killing occurred or the animal's death was noted;

(*5*) The date, time of day, and the day of the study when gross necropsy was performed;

(*6*) The date and day of the study when the histopathology examination was performed; and

(*7*) The reasons for failure (if there was failure) to perform necropsy or histopathology examination.

(B) *Toxic, pharmacologic, and behavioral effects.* In tabular form, data must be provided showing, for each animal:

(*1*) Its identification number;

(*2*) The date of observation of each sign of toxicity or pharmacological effect or behavioral abnormality; and

(*3*) A description of the toxic sign, pharmacological effect, or behavioral abnormality. If such a response occurred repeatedly, it need be described only once and may thereafter be described by reference.

(C) *Food and body weight data.* In tabular form, data must be provided showing, for each animal:

(*1*) Its identification number;

(*2*) Estimated food consumption measured at weekly intervals for the first 13 weeks and at monthly intervals throughout the remainder of the test period; and

(*3*) Body weight measured at least weekly during the first 13 weeks of the test period and biweekly throughout the remainder of the test period.

(D) *Descriptions of tumors and other lesions.* Data must be submitted in an appropriate form showing:

(*1*) For each animal, its identification number, the number of weeks on study, its age (in weeks) at death, the manner of death (terminal kill, moribund, or other), and a complete description and diagnosis of every neoplasm, pre-neoplastic lesion, and non-neoplastic lesion found in the animal. The description and diagnosis must include the time of first observation for each lesion, correlation of the histopathology findings with the clinical and gross necropsy observations, and identity of any neoplasm or other lesion, which may have caused the animal to be moribund or to die. All pre-neoplastic and non-neoplastic lesions observed frequently or common in both treated and control animals must be graded. A commonly-accepted scale such as ±1, 2, 3 and 4 expressing degrees ranging from very slight to extreme may be used; however, other scales reflecting this concept are also acceptable. If a grading system is used, a description of the system must be submitted. The description and diagnosis of individual tumors must distinguish between apparently benign and apparently malignant tumors. Histopathologic abnormalities observed repeatedly in a specific test group need to be described only once, in detail as described above; subsequently, the repeat lesion may be referenced to the complete description. However, significant variations from the detailed description must be noted;

(*2*) For each animal, its identification number, and a list of the tissues examined, with designation by checkmark of those tissues found to be normal;

(*3*) For each animal, its identification number, and the number observed of each of the following: non-neoplastic lesions, pre-neoplastic lesions, benign tumors, and malignant tumors.

(ii) *By test group.* The following information must be arranged by test group (species, dose level and sex) and presented in the format specified. All averages must be accompanied by standard deviation. The number of data units on which a calculation is based must be reported for all percentages and means.

(A) *Toxic, pharmacologic, and behavioral effects.* In tabular form, data must be provided showing, for each test group (dose level and sex): (*1*) A list of each sign of toxicity, pharmacological

effect, or behavioral abnormality affecting any animal in the test group;

(*2*) For each such response, the number of animals affected;

(*3*) For each such response, the median time from the beginning of the study to the first observation of such response; and

(*4*) The median age at death for those animals displaying each type of response.

(B) *Food and body weight data, means.* In tabular and graphic form, data must be provided showing, for each test group (dose level and sex): (*1*) Mean estimated food consumption measured at weekly intervals for the first 13 weeks and at monthly intervals throughout the remainder of the test period; and

(*2*) Mean body weight measured weekly during the first 13 weeks of the test period and bi-weekly throughout the remainder of the test period.

(C) *Survival and kill data.* In tabular format, data must be provided showing, for each test group: the number of animals which remained alive at the end of each 7-day interval, the number of animals that were killed or otherwise died during each 7-day interval, and the number that died by sacrifice and were moribund before sacrifice.

(D) *Clinical laboratory data.* (*1*) In any apropriate form, data must be submitted showing, for each animal: (*i*) Its identification number;

(*ii*) The results of any hematological blood chemistry, and other clinical laboratory tests performed; and

(*iii*) The results of any residue analysis, if performed.

(*2*) In any appropriate form, data must be submitted showing, for each test group (dose level and sex): (*i*) The average of the results of each hematological, blood chemistry, and other clinical laboratory test performed; and

(*ii*) The average results of any residue analysis, if performed.

(E) *Gross necropsy data.* The following test information, arranged by test group (dose level and sex), must be supplied in tabular form: (*1*) Data showing the identification number of any animal in which any gross abnormality was noted, and including, for each such animal, a description of each gross abnormality, the dimensions of any visible lesion, and the data (if known) when it was first observed. Gross abnormalities observed repeatedly in necropsies of the test animals need be described by reference.

(*2*) Data showing the number of animals in which any specific types of gross abnormalities are observed.

(*3*) Data showing the identification number of each animal, individual organ weights, and organ-to-body weight ratios.

(*4*) Data showing the mean weights of each type of organ, the mean organ-to-body weight ratios, and corresponding standard deviations.

(F) *Incidence of tumors, by test group.* Data must be submitted in tabular form, showing: (*1*) For each test group, the number of animals at the start of the test, the number and percentage of animals surviving to the termination of the test, the number and percentage of animals in which any tumor was found, the number and percentage of animals with multiple tumors (more than one type), and the number and percentage of animals with a malignant tumor; and

(*2*) For each type of tumor, the number of animals in each test group in which the affected tissue was examined microscopically, and the number and percentage of animals in each test group in which that type of tumor was observed.

(G) *Incidence of lesions other then tumors, by test group.* References to lesions in this paragraph (k) refer to lesions other than tumors. Data must be submitted in tabular form showing, for each test group: *(1)* The number of animals at the start of the test, the number of animals surviving to the termination of the test, the number of animals in which any lesion was found, the number of animals in which any pre-neoplastic lesions were found, and the number of animals in which any non-neoplastic lesions were found; and

(2) The number of animals affected by each different type of lesion, the average grade (when applicable) of each type of lesion, the number of animals examined microscopocally for each type of lesion, and the percentage of those animals examined which were affected by each type of lesion.

(H) *Cumulative mortality and cumulative incidence of tumors and other lesions at weekly intervals, by test group.* Data must be submitted in tabular form showing, for each test group at each 7-day interval: *(1)* Cumulative mortality (total number of animals which died during the study);

(2) Cumulative incidence of all types of tumors (total number of animals with any type of tumor);

(3) Cumulative incidence of specific types of tumors by site which were observed frequently (total number of animals with a specific type of commonly-occurring tumor); and

(4) Cumulative incidence and average grade (when applicable) for specific types of commonly-occurring non-neoplastic lesions.

(I) *Tumors and other lesions in historical controls.* In an appropriate form, data must be submitted showing the types, incidence (number and percentages), and grades (where known and appropriate) of non-neoplastic and pre-neoplastic lesions and benign and malignant tumors in historical controls (to the extent that such contols were taken into account in evaluating the results of testing).

(iii) *Study evaluation.* (A) An evaluation of the test results, including their statistical analysis, must be made and supplied, based on clinical findings, gross necropsy findings, and histopathology results. This submission must include an evaluation of the relationship, if any, between the animal's exposure to the test substance and the development of benign and malignant neoplasms as well as non-neoplastic disease.

(B) The statistical methods used must be described. This includes survival correction for tumor incidence.

(3) *Summary and analysis of test results.* This section of the test report must contain a summary and analysis of the data, and a statement of the conclusions drawn from the analysis. The summary must highlight any and all positive data or observations, and any deviations from control data which may be indicative of toxic effects. The summary must be presented in sufficient detail to permit independent evaluation of the results.

Appendix A—Dietary Requirements and Contaminant Analysis

Dietary Requirements. This Appendix provides dietary requirements and contaminant analysis of feeds and vehicles for the Chronic Effects Test.

(a) *Nutrient Requirements.* The diet used must be manufactured from the following ingredients and no others. (Reference: Nutrient Requirements of Laboratory Animals, Third Revised Edition, National Academy of Sciences, Washington, D.C., 1978.)

(1) *Ingredients*

Fish meal
Soybean meal
Alfalfa meal
Corn gluten meal
Ground whole wheat
Ground #2 yellow shelled corn
Ground whole oats
Wheat middlings
Brewers dried yeast
Soy oil
Salt
Dicalcium phosphate
Ground limestone

(i) A vitamin premix must be prepared from the following vitamin sources:

Vitamin A Palmitate or Acetate
D activated animal sterol
Menadione activity
Alpha-tocopherol acetate
Choline Chloride
Folic Acid
Niacin
d-Calcium Pantothenate
Riboflavin Supplement
Thiamine mono nitrate
B12 Supplement
Pyridoxine hydrochloride
d-Biotin

A mineral premix must be prepared from the following compounds:

Cobalt carbonate
Copper sulfate
Iron sulfate
Magnesium oxide
Manganese oxide
Zinc oxide
Calcium iodate

Microanalysis—The total calculated concentration of nutrients in the diet are from the ingredients and from the vitamin and mineral fortifications at the time of manufacture must be as follows:

	Minimum (percent)
Crude protein	18.0
Crude fat	4.0
Crude fiber	4.2
Ash	8.0

Nutrient concentrations in final diet must not vary from the individually stated values by more than 10%.

Amino Acids (percent of total diet):	*Minimum*
Arginine	0.95
Lysine	.90
Methionine	.38
Cystine	.27
Tryptophan	.20
Glycine	1.00
Histidine	.38
Leucine	1.50
Isoleucine	.95
Phenylalanine	.90
Tyrosine	.80
Threonine	.85
Valine	.95

Minerals:	Minimum
Calcium	1.15 percent
Phosphorous	.90 percent
Potassium	.80 percent
Sodium	.33 percent
Magnesium	.20 percent
Iron	345 mg/kg
Zinc	50 mg/kg
Manganese	140 mg/kg
Copper	12 mg/kg
Cobalt	.80 mg/kg
Iodine	1.85 mg/kg

	Minimum	Maximum
Vitamins:		
Vitamin A	15.0	75.00 IU/g
Vitamin D	4.0	10.00 IU/g
Alpha-tocopherol	50.0	mg/kg
Thiamine	14.0	mg/kg
Riboflavin	7.0	mg/kg
Niacin	65.0	mg/kg
Pantothenic Acid	32.0	mg/kg
Choline	1900.0	mg/kg
Pyridoxine	10.0	mg/kg
Folic Acid	2.0	mg/kg
Biotin	0.3	mg/kg
Vitamin B12	14.0	Mcg/lb
Vitamin K	3.0	mg/kg
For autoclavable diet:		
Vitamin A	30.0	mg/kg
Thiamin	70.0	mg/kg
Vitamin K	20.0	mg/kg

The diet must be void of any feed additives containing antibiotics or estrogen activity. When diet is purchased for feeding in meal form, it must be manufactured by regrinding pellets.

(2) *Approximate Analysis*—Analysis for nutrient content of both ingredients and the finished product must be conducted in accordance with the procedures of the Association of Official Agricultural Chemists (1975) and must be expressed as a nutrient content percentage by weight on an air-dry basis.

(3) *Ingredient Standards*—Ingredients used in the manufacture of this ration must not be contaminated with any more than 3 percent of foreign materials such as other grains, weed seeds, chaff, etc. Nor will any mold, must, or insect/rodent infestation be allowed. The average minimum nutrient concentrations of ingredients used in the manufacture of this ration must be equal to the values published in the National Academy of Sciences Publication 1684, United States-Canadian Tables of Food Composition.

The data from these analyses must be made available to the facility using the product.

(4) *Feed Additives and Processing Restrictions*—The product must contain no antibiotics, other preservatives or estrogen additives of any kind. All milling and warehousing conditions and/or restrictions, as specified in the latest issue of the National Institues of Health Standard No. 1, apply to the feed covered by this specification. The product must not be altered in any manner that will affect the final nutrient content.

(5) *Labeling*—Each bag must be clearly marked with the name of the product, the name of the manufacturer, the net weight, the ingredients, the guaranteed analysis of its contents, the date (month, day, and year) the manufacturing process was completed, and the batch number under which it was processed.

(b) *Contaminant analysis of feeds and vehicles.*

Parameter	Specification limitation	
	Minimum	Maximum
Aflatoxin (B1, B2, G1, G2) ppb Total		5
Estrogenic Activity, ppb (DES eq.)		1
Lindane, ppb		20
Heptachlor, ppb		20
Malathion, ppm		2.5
DDT (Total), ppb		100
Dieldrin, ppb		20
Cadmium, ppb		160
Arsenic, ppm		1.0
Lead, ppm		1.5
Mercury, ppb		100
Selenium, ppm	0.1	0.6
PCB, ppb		50
Nitrosamines, ppb		10

§ 772.113–2 Oncogenic effects test standards.

(a) *Study design.* (1) Species and Stains.

(2) Sex.

(3) Age at Start of Test.

(4) Group Size.

(5) Control Groups.

(6) Route(s) of Administration.

(7) Frequency of Exposure.

(8) Duration of Treatment and Observation Periods.

(9) Dose Levels and Dose Selection.

(b) *Study conduct.* (1) Clinical Procedures.

(2) Pathology Procedures.

§ 772.113–2 Oncogenic effects test standards.

(a) *Study design.* (1) *Species and Strain.* (i) The tester must use at least two rodent species, the laboratory mouse and rat. An alternative species may be used if the sponsor can provide sufficient data and/or rationale to demonstrate that it is a more appropriate species for a specific test substance. The sponsor must present such data and/or rationale for Agency approval as a part of the study plan submission.

(ii) The sponsor or tester must select the specific strains and/or stocks of test animals to be used. Established strains and/or stocks which are expected to be sensitive to the test substance must be used. As part of the study plan submission, the sponsor must present the rationale for selection of the specific test animals. This must include a summary of any prior test results with the selected species, historical data on their lifespans, spontaneous diseases and conditions (including tumors) and their incidences.

Note.—Acceptable rationale for alternate species would be results from prior oncogenicity studies which show that the alternative species is sensitive to the oncogenic effects of the chemical class to which the test substance belongs or that the alternate species has similar metabolism or pharmacokinetics to humans.

(2) *Sex.* The tester must use equal numbers of males and females at each dose level.

(3) *Age at start of test.* The tester must begin to dose rodents as soon as possible after weaning and environmental acclimatization, by no later than six (6) weeks of age. For nonrodents, the Agency must approve the age of initial exposure.

(4) *Group size.* Each "test group" of rats or mice must contain at least 50 animals. The tester must assign animals to individual test groups by a specified randomization procedure. When the study plan calls for interim kill, the tester must increase the number of animals in each group at the start of the study by the number scheduled to be killed before completion of the study. If species other than the laboratory mouse

and rat are selected, EPA must approve the number of animals per group.

(5) *Control groups.* A tester must use a matched control group which is identical in every respect to the exposed groups except for exposure to the test substance.

Note (i).—If a vehicle is administered to the matched control group and if its toxic properties are not known, the tester may, at his/her discretion, use a negative or untreated control group.

Note (ii).—The EPA may require a Positive Control Group for particular chemicals when the sensitivity of the test animal to the chemical class to which the test substance belongs cannot be documented. When used, the positive control group should serve as an internal quality control to ascertain whether the test animals are sensitive to or respond in a predictable manner to known toxic agents and whether the test strain or species reacts similarly to another strain or species when exposed to the same known standard toxicant.

(6) *Route(s) of administration.* To the extent possible, route(s) of administration should be comparable to the expected or known routes of human exposure. The test rules in Part 771 will specify the route(s) to be employed for a particular chemical. For inhalation and dermal studies, Part 771 will also specify the specific conditions for administering the test substance.

(7) *Frequency of exposure.* The tester must administer test substance and vehicle, if any, by the same route and at the same frequency for the duration of the study. For gavage, the test substance must be administered daily; for feeding, *ad libitum;* for inhalation exposure, a minimum of 5 days per week, 6 hours per day; and for dermal exposure, as specified in the applicable test rule. The tester must conduct the dosing at approximately the same time each day.

(8) *Duration of treatment and observation periods.* The tester must administer the test substance to rodent species for a minimum of 24 months but no longer than 30 months. If a nonrodent species is used, the Agency must approve the duration of exposure.

(9) *Dose levels and dose selection.* (i) The tester must provide data from at least three dose levels (in addition to controls) in each sex of each species.

(A) The high dose level must be the maximum level that can be administered for the duration of the test period, with demonstrable but only slight toxicity, and no substantial reduction in longevity due to effects other than tumors. Signs of demonstrable, slight toxicity are a weight decrement not to exceed 10 percent compared to appropriate controls, clinical signs of toxicity, or pathologic lesions other than those related to a neoplastic response.

(B) The intermediate dose level must be some fraction (¼ to ½) of the high dose level.

(C) The lowest dose level must be some fraction (½ or less) of the intermediate dose level but not less than 10 percent of the high dose level.

(D) The sponsor or tester may add additional dose levels at his/her own discretion. If other dose levels are tested, the sponsor must submit the data from any such discretionary levels to Agency along with that of the required levels.

(ii) The tester must conduct a preliminary toxicology study of at least 90 days to select the chronic dose levels which will meet the requirements in this subsection. A preliminary toxicology study of at least 90 days that has been completed previously may be submitted for this purpose.

(iii) The sponsor must submit the rationale for dose selection including supporting data from preliminary toxicity studies as a part of the plan submission.

(b) *Study conduct.* (1) *Clinical procedures.* Veterinarians, as specified in § 772.113–1(e)(2), must ascertain and be responsible for the health status and care of all test animals prior to and during the study. Technical employees, as specified in § 772.113–1(e)(3)(ii), must be responsible for the daily observations and care of test animals.

(i) *Observation of Animals.* (A) Each test animal must be identified by a specific identification number. The tester must account for all animals at the end of the study. The tester must establish and adhere to standard operating procedures for housing, feeding, handling, and care of test animals as specified in § 772.110–1, Subpart B. To further assure minimal loss of animals due to cannibalism or autolysis of tissue, technical employees, as specified above, must observe the test animals every 12 hours throughout the test period. EPA may consider a study to be unacceptable for purposes of satisfying a test rule requirement if losses in any test group exceed 5 percent.

(B) Technical employees must conduct routine clinical examinations on each animal. These clinical examinations must include weighing of each animal, approximately the same time of day, at least once a week during the first 13 weeks, and every two weeks thereafter, and observing animals in relation to food and water consumption, morbidity, mortality and causes thereof, loss of animals for whatever reason, signs to toxicity, pharmacologic effects, and behavioral changes. The observer must record all data in detail at the time of observation.

(ii) *Hematology.* The tester must conduct the following quantitative hematologic determinations on a minimum of eight predesignated animals in each test group at one year (± one month) and at termination: hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts, platelet count, and prothrombin and clotting times. If hematologic evidence of anemia is present at one year, reticulocyte counts must be performed within one week of the determination. In addition to the tests listed above, if any interim clinical observations suggest that other tests are necessary to assess the health status of test animals, the appropriate tests must be conducted. In the event that any of the predesignated animals does not survive 12 months, another animal selected by statistical randomization from the remainder of the appropriate test group can serve as a replacement.

Note.—Predesignated means that the animal has been selected to undergo this test by a specified randomization procedure prior to initiation of the study.

(iii) *Interim kill.* The tester may kill predesignated animals (other than those predesignated for hematological test in paragraph (b)(1)(ii) of this section at any time during the study, provided that he (she) increased the number of animals started in the study at least by the number scheduled or anticipated to be killed before the end of the study.

(iv) *Killing of test animals.* Animals which appear during the study as moribund, injured, or weak, and not expected to survive to the next observation, must be killed to preclude the loss of tissues from cannibalism and/or autolysis. Animals surviving to the termination of the study must also be killed. A technical employee must obtain blood samples for hemotologic determinations from each animal immediately before it is killed or as it is killed. The method used for killing must be humane and the same throughout the study. The tester must select a method of killing which will not produce interfering pathologic lesions.

(2) *Pathology procedures.* A Board-certified or Board-eligible pathologist, as specified in § 772.113–1(e)(1)(i), must be responsible for the planning and conduct of all pathology procedures and histopathology examinations, as well as for the final interpretation of all pathology data. Other doctorate pathologists, as specified in § 772.113–

1(e)(1)(ii), are also acceptable for conducting procedures in their disciplines of specialization, under the direct supervision of a Board-Certified or Board-Eligible pathologist as specified in § 772.113–1(e)(1)(i).

Note.—Direct supervision means that the supervisor is immediately available for consultation, as necessary. This consultation may be done in person or by telephone.

(i) *Gross necropsy.* (A) Qualified pathologists, as specified in § 772.113–1(e)(2)(1), must perform or personally supervise the necropsies. Other appropriately trained technical employees, as specified in § 772.113–1(e)(3)(i), may assist in the necropsy.

Note.—Personal supervision means that the supervisor is immediately available for consultation at the site.

(B) Animals must be necropsied as soon as possible after death but no later than 16 hours after death. If necropsy cannot be performed immediately after the animal is killed or found dead, a technical employee must immediately refrigerate (but not freeze) the animal at temperatures low enough to minimize tissue autolysis (4–8° C). Animals found dead upon routine clinical examination must be necropsied as soon as possible to salvage useable tissues.

(C) The gross necropsy must include an initial physical examination of the external surfaces and all orifices followed by an internal examination of tissues and organis *in situ*. The examination must include the following: external and internal portions of all hollow organs; cranial cavity and external surfaces of the brain and spinal cord; nasal cavity and paranasal sinuses; neck with its associated organs and tissues; thoracic, abdominal, and pelvic cavities with their associate organis and tissues; and the muscular/skeletal carcass. The urinary bladder and lungs must be inflated with a proper fixative to allow for better gross examination and preservation.

(D) The person responsible for the gross necropsy must record all gross necropsy findings in accordance with § 772.113–1 (k)(2).

(ii) *Tissue preservation.* A technical employee must immediately preserve all tissues and organs from all test animals in ten percent (10%) buffered formalin or another recognized and accepted fixative appropriate for the specific tissue(s). Sections from the following tissues from all test animals regardless of their time of death must be properly preserved for routine microscopic examination:

(A) All gross lesions (with a margin of normal tissue);

(B) Brain (minimum of one section each from the forebrain, midbrain, and hindbrain);

(C) Eyes and contiguous Harderian glands;

(D) Pituitary gland:

(E) Major salivary glands, thymus, thyroid with parathyroid, mammary glands; Zymbal's gland (if present);

(F) Oral mucous membrane (including random sections from tongue, buccal, and alveolar mucosa, pharynx, and nasopharynx);

(G) Heart and aorta;

(H) Trachea; lungs with the mainstem bronchi;

(I) Esophagus, stomach, small intestines and large intestine (cecum, colon, and rectum);

(J) Adrenal glands, pancreas, liver (minimum of two lobes), gall bladder (if present), spleen;

(K) Kidneys, urinary bladder;

(L) Representative lumph nodes (including those draining any neoplasm and those with gross changes);

(M) Bone including marrow from the sternum, vertebra and/or tibiofemoral joint;

(N) Skeletal muscle;

(O) For males: testes, prostate, and all other accessory sex organs;

(P) For females: vagina, corpus and cervix uteri, ovaries, and fallopian tubes.

(iii) *Preparation of tissue for microscopic examination.* A pathologist or a technical employee, as specified in § 772.113–1(e)(3)(i), must prepare all specimens for microscopic examination.

(A) *Tissue fixation and trimming.* A technical employee must fix tissues for the appropriate time for the fixative utilized. A pathologist must perform or directly and personally supervise tissue trimming. Routinely, tissues must be trimmed to a thickness of no more than 0.4 cm for subsequent processing. Parenchymal organs must be trimmed to allow for the largest surface area possible for subequent microscopic examination. Hollow organs must be trimmed to allow for a cross section mount from mucosa to serosa. Lymph nodes must be bisected through the hilus, if possible.

(B) *Slide preparation.* A technical employee must cut tissues routinely at a thickness of three to six micra (3 to 6 μ), in no case exceeding 10μ. All tissues must be stained routinely with hematoxylin and eosin (H&E). EPA encourages the use of special stains appropriate to the specific neoplasm, lesion, or tissue. Multiple sections (step cuts) must be made on each tissue or organ that contains gross evidence of a neoplasm or lesion and on each tissue or organ in which a metastasis may be anticipated. The tester must identify all blocks and microscopic slides by references to the animal's specific identification number and must preserve and hold them in accordance with § 772.110–1(j)(2).

(iv) *Microscopic examination and evaluation.* (A) Qualified pathologists as described in § 772.113–1(e)(1), must perform the microscopic examination and evaluation with subsequent diagnosis. The same pathologist must examine and evaluate all microscopic slides from all test animals of a given species.

(B) Microscopic examination must be performed on all tissues described in paragraphs (b)(2)(ii), (b)(2)(v), and (b)(2)(vi) of this section. The pathologist must record, document, and report all microscopic findings including all abnormalities, lesions, neoplasms, metastatic tumors and their anatomic locations in accordance with § 772.113–1(k)(2).

(v) *Additional examination.* All adverse health effects, including non-oncogenic effects, observed during the course of the study must be examined. When there is clinical evidence suggesting specific toxicologic or pharmacologic effects, including non-oncogenic effects, the necropsy and microscopic examinations of the suspected target organs must be conducted in greater detail. For example, when there is clinical evidence of neurologic effects, multiple sections from brain, spinal cord, and nerves must be examined.

(vi) *Special examinations.* (A) Additional sections, as specified below, must be microscopically examined from a minimum of ten animals selected randomly from the long-term survivors of each test group and in all animals in which clinical or grossly observable evidence of disease is present. If microscopic examination reveals evidence of disease in any of the tissues, then these target tissues must be examined in all test animals.

(B) The necropsy and microscopic examinations must include, in addition to those tissues listed in paragraph (b)(2)(ii) of this section, the following:

(*1*) *In a feeding study:* nasal cavity; paranasal sinuses; nasopharynx.

(*2*) *In an inhalation study:* multiple sections of the upper respiratory tract; nares; nasal cavity; paranasal sinuses; hypopharynx-larynx.

(*3*) *In a dermal study:* skin (normal); skin from sites of skin painting.

§ 772.113–3 Non-oncogenic chronic effects test standards.

(a) *Study design.* (1) Species and strains.

(2) Sex.

(3) Age at start of test.

(4) Group size.

(5) Control groups.

(6) Route(s) of administration.

(7) Frequency of exposure.

(8) Duration of treatment and observation periods.

(9) Dose levels and dose selection.

(b) *Study conduct.* (1) Clinical procedures.

(2) Pathology procedures.

§ 772.113–3 Non-oncogenic chronic effects test standards.

(a) *Study design.* (1) *Species and strains.* (i) The tester must use at least two mammalian species: one, a laboratory rat and the second, a nonrodent. The Agency recommends the dog as the nonrodent species. The tester may utilize other suitable nonrodent species approved by EPA.

Note.—Selection of the most appropriate nonrodent species should be predicated upon such factors as metabolism, pharmacokinetics, sensitivity or organotropism and other considerations pertinent to the study.

(ii) The sponsor or tester must select the specific strains and/or stocks of test animals to be used. Test animals must be from established strains and/or stocks. As part of the study plan submission, the sponsor must present the rationale for selection of the specific test animals along with historical data on their lifespans and disease types and incidences.

(2) *Sex.* The tester must use equal numbers of males and females at each dose level.

(3) *Age at start of test.* The tester must begin to dose as soon as possible after weaning and environmental acclimatization, but no later than six weeks of age for rodents and at ten weeks of age for dogs. For nonrodent species, other than the dog, the Agency must approve the age of initial exposure.

(4) *Group size.* Each "test group" of rodents must contain at least 50 animals (plus at least 8 additional for clinical laboratory testing). If the nonrodent species is the dog, then each group must contain at least six animals. The tester must assign animals to individual test groups by a specified randomization procedure. When the study plan calls for interim kill, the tester must increase the number of animals in each group at the start of the study by the number scheduled to be killed before completion of the study. If species other than the laboratory dog and rat are selected, EPA must approve the number of animals per group.

(5) *Control groups.* A tester must use a matched control group which is identical in every respect to the exposed groups except for exposure to the test substance.

Note (i).—If a vehicle is administered to the matched control group and if its toxic properties are not known, the tester may, at his/her discretion, use a negative or untreated control group.

Note (ii).—The EPA may require a Positive Control Group for particular chemicals when the sensitivity of the test animal to the chemical class to which the test substance belongs cannot be documented. When used, the positive control group should serve as an internal quality control to ascertain whether the test animals are sensitive to or respond in a predictable manner to known toxic agents and whether the test strain or species reacts similarly to another strain or species when exposed to the same known standard toxicant.

(6) *Route(s) of administration.* To the extent possible, route(s) of administration should be comparable to the expected or known routes of human exposure. Test rules in Part 771 will specify the route(s) to be employed for a particular chemical. For inhalation and dermal studies, Part 771 will also specify the specific conditions for administering the test substance.

(7) *Frequency of exposure.* The tester must administer test substance and vehicle, if any, by the same route and at the same frequency for the duration of the study. For gavage, the test substance must be administered daily; for feeding, *ad libitum;* for inhalation exposure, a minimum of 5 days per week, 6 hours per day; and for dermal exposure, as specified in the applicable test rule. For gavage, the tester must conduct the dosing at approximately the same time each day.

(8) *Duration of treatment and observation periods.* The tester must administer the test substance to rate for at least 30 months. In studies with nonrodents, the tester must test for at least 2 years unless the Agency authorizes specific exceptions.

(9) *Dose levels and dose selection.* (i) The tester must select doses to permit analysis of dose-response relationships and the "no observable effect level" (NOEL).

(A) A minimum of three dose levels (in addition to controls) in each sex of each species must be used.

(B) The highest dose level must demonstrate toxicologic effects. Mortality in rat groups must not exceed 50 percent before 18 months. Mortality in nonrodent groups must be kept to a minimum but significant toxicologic effect must also be demonstrated in the species.

(C) The lowest dose level must be selected to produce no observable evidence of toxicity other than tumors (NOEL).

(D) The sponsor or tester may add additional dose levels at his/her own discretion. If other dose levels are tested, the sponsor must submit the data from any such discretionary levels to the Agency along with that of the required levels.

(ii) The tester must conduct a preliminary toxicology study of at least 90 days to select the chronic dose levels which meet the requirements of this section. A preliminary toxicology study of at least 90 days that has been completed previously may be submitted for this purpose.

(iii) The sponsor must submit the rationale for dose selection including supporting data from preliminary toxicity studies as a part of the study plan submission.

(b) *Study conduct.* (1) *Clinical procedures.* A veterinarian, as specified in § 772.113–1(e)(2), must ascertain and be responsible for the health status and care of all test animals during the study. A technical employee, as specified in § 772.113–1(e)(3)(ii), must be responsible for the daily observations and care of the test animals.

(i) *Observation of animals.* (A) Each test animal must be identified by a specific identification number. The tester must account for all animals at the end of the study. The tester must establish and adhere to standard operating procedures for housing, feeding, handling, and care of test animals as specified in § 772.110–1. To further assure minimal loss of animals due to cannibalism or autolysis of tissue, technical employees, as specified above, must observe the test animals at least every 12 hours throughout the test period. EPA may consider a study to be unacceptable for purposes of satisfying a test rule requirement if losses in any test group exceed 5 percent.

(B) Technical employees must conduct routine clinical examinations on all test animals. Clinical examination must include weighing of each animal, at approximately the same time of day, at least once a week during the first 13 weeks, and every two weeks thereafter and observing all animals in relation to food and water consumption, morbidity, mortality and causes thereof, loss of animals for whatever reason, signs of toxicity, pharmacologic effects, and behavioral changes. The observer must

record all data in detail at the time of observation.

(ii) *Clinical laboratory testing.* The tester must conduct the following quantitative determinations on a minimum of eight additional predesignated rats in each test group. For nonrodents, all animals in each test group must be utilized. In addition to the tests listed below, if any interim clinical observations suggest that other tests are necessary to assess the health status of test animals, the appropriate tests must be conducted.

Note.—Predesignated means that the animal has been selected to undergo these tests by a specified randomization procedure prior to initiation of the study.

(A) *Hematology.* The tester must conduct the following quantitative hematologic determinations at least at 3, 6, 12, 18, 24 months and at study termination: hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts, platelet count, and prothrombin and clotting times. If hematologic evidence of anemia is present, reticulocyte counts must be performed within one week of the determination.

(B) *Blood chemistry.* The tester must conduct the following quantitative blood chemistry determinations at least at 3, 6, 12, 18, 24 months and at study termination: calcium, sodium, potassium, chloride, serum lactic dehydrogenase, serum glutamic pyruvic transaminase, creatinine kinase, serum glutamic oxaloacetic transaminase, glucose, blood urea nitrogen, creatinine, direct and total bilirubin, cholinesterase, total cholesterol, triglycerides, serum alkaline phosphatase, albumin, globulin, and total protein. In addition to these tests, the tester may conduct other quantitative blood chemistry determinations at his/her discretion, such as uric acid, gammaglutamyl transpeptidase, and ornithine carbamoyltransferase.

(C) *Urinalysis.* The tester must conduct the following quantitative determinations at least at 3, 6, 12, 18, 24 months and at study termination: specific gravity or osmolarity, pH, protein, glucose, ketones, bilirubin, and urobilinogen, as well as microscopic examination and analysis of formed elements. Each animal's urine must be evaluated individually.

Note.—*Additional Tests.* Based on results of concurrent or previous studies on the test substance, its metabolic or degradation products, the tester should conduct such other determinations as may be necessary for adequate toxicological evaluation.

(D) *Function tests.* (*1*) The tester must determine the functional capacity of the renal, hepatic, pulmonary, and cardiovascular systems.

Note.—Additional determinations must place major emphasis on organ or system function tests. Selection of the appropriate tests must be based upon the findings in the subchronic studies or observations made during the course of present study.

(*2*) Additional quantitative determinations may include, but not necessarily be limited to the following: water dilution and water concentration tests for renal function; total lung capacity, functional residual capacity, and residual volume for pulmonary function; bromsulphalein excretion test for liver function; electrocardiogram, blood pressure, and exercise recovery for cardiovascular function. The tester must perform these evaluations at the beginning (nonrodent only) and at least every 3, 6, 12, 18, 24 months and at study termination.

(E) *Residue analysis.* The tester must measure levels of test substance, major metabolites or other biologically significant metabolites at 3, 6, 12, 18, and 24 months ± 1 month and at the termination of the study. Tissues from the predesignated animals analyzed should include all target tissues from prechronic toxicology studies and those suggested by pharmaco-kinetic studies. These analyses must include at least plasma, 24-hour urine, feces and, at time of death or scheduled killing, liver and kidney.

(iii) *Interim kill.* The tester may kill predesignated animals (other than those predesignated for hematological tests in paragraph (b)(1)(ii)(A) of this section at any time during the study, provided that he/she increases the number of animals started in the study at least by the number scheduled or anticipated to be killed before the end of the study.

(iv) *Killing of test animals.* Animals which appear during the study as moribund, injured, or weak, and not expected to survive to the next observation, must be killed to preclude the loss of tissues from cannibalism and/or autolysis. Animals surviving to the termination of the study must also be killed. A technical employee must obtain blood samples for hematologic determinations from each animal immediately before it is killed or as it is killed. The method used for killing must be humane and the same throughout the study. The tester must select a method of killing which will not produce interfering pathologic lesions.

(2) *Pathology procedures.* A Board-Certified or Board-Eligible pathologist, as specified in § 772.113–1(e)(1)(i), must be responsible for the planning and conduct of all pathology procedures and histopathology examination, as well as for the final interpretation of all pathology data. Other doctorate pathologists, as specified in § 772.113–1(e)(1)(ii), are also acceptable for conducting procedures in their disciplines of specialization, under the direct supervision of a Board-Certified or Board-Eligible pathologist as specified in § 772.113–1(e)(1)(i).

Note.—Direct supervision means that the supervisor is immediately available for consultation, as necessary. This consultation may be done in person or by telephone.

(i) *Gross necropsy.* (A) Qualified pathologists, as specified § 772.113–1(e)(1), must perform or personaally supervise the necropsies. Other appropriately trained technical employees, as specified in § 772.113–1(e)(3)(i) may assist in the necropsy.

Note.—Personal supervision means that the supervisor is immediately available for consultation at the site.

(B) Animals must be necropsied as soon as possible after death but no later than 16 hours after death. If necropsy cannot be performed immediately after the animal is killed or found dead, a technical employee must immediately refrigerate (but not freeze) the animal at temperatures low enough to minimize tissue autolysis (4–8° C). Animals found dead upon routine clinical examination must be necropsied as soon as possible to salvage usable tissues.

(C) The gross necropsy must include an initial physical examination of the external surfaces and all orifices followed by an internal examination of tissues and organs *in situ.* The examination must include the following: external and internal portions of all hollow organs; cranial cavity and external surfaces of the brain and spinal cord; nasal cavity and paranasal sinuses; neck with its associated organs and tissues; thoracic, abdominal, and pelvic cavities with their associated organs and tissues; and the muscular/skeletal carcass. The urinary bladder and lungs must be inflated with a proper fixative to allow for better gross examination and preservation.

(D) The weights of the heart, liver, kidneys, testes, spleen, lung, brain, and adrenals must be recorded after careful dissection and trimming. In addition, the thyroid (with parathyroids) and pituitary must be weighed for each nonrodent. The person responsible for the gross necropsy must record all gross necropsy findings in accordance with § 772.113–1(k)(2).

(ii) *Tissue preservation.* A technical employee must immediately preserve all tissues and organs from all test animals in 10 percent buffered formalin or another recognized and accepted fixative appropriate for the specific tissue(s). Sections from the following tissues from all test animals regardless of their time of death must be properly preserved for routine microscopic examination:

(A) All gross lesions (with a margin of normal tissue);

(B) Brain (minimum of one section each from the forebrain, midbrain, and hindbrain);

(C) Spinal cord (minimum of one section each from cervical, thoracic, and lumbar regions);

(D) Eyes and contiguous Harderian glands;

(E) Pituitary gland;

(F) Major salivary glands, thymus, thyroid with parathyroid, mammary glands, Zymbal's gland (if present);

(G) Oral mucous membrane (including random sections from tongue, buccal, and alveolar mucosa, pharynx, and nasopharynx);

(H) Heart and aorta (three sections from different locations);

(I) Trachea; lungs, with the mainstem bronchi;

(J) Esophagus, stomach, small intestines and large intestine (cecum, colon, and rectum);

(K) Adrenal glands, pancreas, liver (minimum of two lobes), gall bladder (if present), spleen;

(L) Kidneys, urinary bladder;

(M) Representative lymph nodes (including those draining any neoplasm and those with gross changes);

(N) Bone including marrow, from the sternum vertebra and/or tibiofemoral joint;

(O) Skin (sections from similar sites of all animals);

(P) Skeletal muscle;

(Q) For males: testes, prostate, and all other accessory sex organs;

(R) For females: vagina, corpus and cervix uteri, ovaries, and fallopian tubes.

(iii) *Preparation of tissue for microscopic examination.* A pathologist or a technical employee, as specified in § 772.113–1(e)(3)(i), must prepare all specimens for microscopic examination.

(A) *Tissue fixation and trimming.* The technical employee must fix tissues for the appropriate times for the fixative utilized. A pathologist must perform or directly and personally supervise tissue trimming. Routinely, tissues must be trimmed to a thickness of no more than 0.4 cm for subsequent processing. Parenchymal organs must be trimmed to allow for the largest surface areas possible for subsequent microscopic examination. Hollow organs must be trimmed to allow for a cross section mount from mucosa to serosa. Lymph nodes must be bisected through the hilus, if possible.

(B) *Slide preparation.* A technical employee must cut tissues routinely at a thickness of three to six micra (3 to 6 μ), in no case exceeding 10 μ. All tissues must be stained routinely with hematoxylin and eosin (H&E). EPA encourages the use of special stains appropriate to the specific neoplasm, lesion, or tissue. Multiple sections (step cuts) must be made on each tissue or organ that contains gross evidence of a neoplasm or lesion and on each tissue or organ in which a metastasis may be aniticipated. The tester must identify all blocks and microscopic slides by reference to the animal's specific identification number and must preserve and hold them in accordance with § 772.110–1(j)(2).

(iv) *Microscopic examination and evaluation.* (A) Qualified pathologists as described in § 772.113–1(e)(1), must perform the microscopic examination and evaluation with subsequent diagnosis. The same pathologist must examine and evaluate all microscopic slides from all test animals of a given species.

(B) Microscopic examination must be performed on all appropriate tissues described in paragraphs (b)(2)(ii), (b)(2)(v), and (b)(2)(vi) of this section. The pathologist must record, document, and report all microscopic findings including all abnormalities, lesions, neoplasms, metastatic tumors and their anatomic location in accordance with § 772.113–1(k)(2).

(v) *Additional Examinations.* All adverse health effects observed during the course of the study must be examined. When there is clinical evidence of specific toxicologic or pharmacologic effects related to specific target organs, the necropsy and microscopic examinations of the suspected target organs must be conducted in greater detail. For example, when there is clinical evidence of neurologic effects, multiple sections from brain, spinal cord, and nerves must be examined.

(vi) *Special Examinations.* (A) Additional sections must be microscopically examined from a minimum of ten rodent animals selected randomly from the long-term survivors and all nonrodent animals of each test group and in all animals in which clincial or grossly observable evidence of disease is present. If microscopic examination reveals evidence of disease in any of these tissues, then these target tissues must be examined in all test animals.

(B) The necropsy and microscopic examination must include, in addition to those tissues listed in paragraph (b)(2)(ii) of this section, the following:

(*1*) *In a feeding study:* nasal cavity; paranasal sinuses; nasopharynx.

(*2*) *In an inhalation study:* multiple sections of the upper respiratory tract; nares; nasal cavity; paranasal sinuses; hypopharynx-larynx.

(*3*) *In a dermal study:* skin (normal); skin from sites of skin painting.

§ 772.113–4 Combined chronic effects test standards.

(a) *Study design.* (1) Species and strains.

(2) Sex.

(3) Age at start of test.

(4) Group size.

(5) Control groups.

(6) Route(s) of administration.

(7) Frequency of exposure.

(8) Duration of treatment and observation periods.

(9) Dose levels and dose selection.

(b) *Study conduct.* (1) Clinical procedures.

(2) Pathology procedures.

§ 772.113–4 Combined chronic effects test standards.

(a) *Study design.* (1) *Species and strains.* (i) The tester must use at least three mammalian species: two rodent species, the laboratory mouse and rat, and a nonrodent. The Agency recommends the dog as the nonrodent species. The tester may utilize other suitable nonrodent species after prior approval by EPA.

Note.—Section of the most appropriate nonrodent species should be predicated upon such factors as metabolism, pharmacokinetics, sensitivity or organotropism and other considerations pertinent to the study.

(ii) The sponsor or tester must select the specific strains and/or stocks of test animals to be used. Test animals must be from established strains and/or stocks. As part of the study plan submission, the sponsor must present the rationale for selection of the specific test animals along with historical data on their lifespans and disease types and incidences.

(3) *Sex.* The tester must use equal numbers of males and females at each dose level.

(3) *Age at start of test.* The tester must begin to dose as soon as possible after weaning and environmental acclimatization, but no later than six

weeks of age for rodents and at ten weeks of age for dogs. For nonrodent species, other than the dog, the Agency must approve the age of initial exposure.

(4) *Group size.* Each "test group" of rodents must contain at least 50 animals (plus at least 8 additional for clinical laboratory testing). If the nonrodent species is the dog, then each group must contain at least six animals. The tester must assign animals to individual test groups by a specified randomization procedure. When the study plan calls for interim kill, the tester must increase the number of animals in each group at the start of the study by the number scheduled to be killed before completion of the study. If species other than the laboratory dog and rat are selected, EPA must approve the number of animals per group.

(5) *Control groups.* A tester must use a matched control group which is identical in every respect to the exposed groups except for exposure to the test substance.

Note (i).—If a vehicle is administered to the matched control group and if its toxic properties are not known, the tester may, at his/her discretion, use a negative or untreated control group.

Note (ii).—The EPA may require a Positive Control Group for particular chemicals when the sensitivity of the test animal to the chemical class to which the test substance belongs cannot be documented. When used, the positive control group should serve as an internal quality control to ascertain whether the test animals are sensitive to or respond in a predictable manner to known toxic agents and whether the test strain or species reacts similarly to another strain or species when exposed to the same known standard toxicant.

(6) *Route(s) of administration.* To the extent possible, route(s) of administration should be comparable to the expected or known routes of human exposure. Test rules in Part 771 will specify the route(s) to be employed for a particular chemical. For inhalation and dermal studies, Part 771 will also specify the specific conditions for administering the test substance.

(7) *Frequency of exposure.* The tester must administer test substance and vehicle, if any, by the same route and at the same frequency for the duration of the study. For gavage, the test substance must be administered daily; for feeding, *ad libitum;* for inhalation exposure, a minimum of 5 days per week, 6 hours per day; and for dermal exposure, as specified in the applicable test rule. For gavage, the tester must conduct the dosing at approximately the same time each day.

(8) *Duration of treatment and observation periods.* The tester must administer the test substance to the laboratory mouse for a minimum of 24 months, but no longer than 30 months and to the laboratory rat for at least 30 months. In studies with nonrodents, the tester must administer the test substance for at least 2 years unless the agency authorizes specific exceptions.

(9) *Dose levels and dose selection.* (i) The tester must select doses to permit the evaluation of oncogenic potential, dose-response relationships, and a "no observable effect level" (NOEL).

(A) In the mouse, the tester must use the dose levels as specified in § 772.113–2 (Oncogenic Effects Test Standards).

(B) In the rat, the tester must use at least four or five dose levels (in addition to controls) in each sex of each species.

(*1.*) The highest dose level must demonstrate toxicologic effects. Mortality in rat groups must not exceed 50 percent before 18 months.

(*2.*) The tester must also include the dose levels as specified in § 772.113–2 (Oncogenicity Test Standards).

(*3.*) One dose level must be selected to produce no observable evidence of toxicity other than tumors (NOEL).

(*4.*) If one of the dose levels required in paragraph B is predicted to induce no observable effects other than tumors (NOEL), a fifth dose is not required.

(C) In the nonrodent, the tester must use the dose levels as specified in § 772.113–3 (Non-Oncogenic Chronic Effects Test Standards).

(ii) The sponsor or tester may add additional dose levels at his/her own discretion. If other dose levels are tested, the sponsor must submit the data from any such discretionary levels to the Agency along with that of the required levels.

(iii) The tester must conduct a preliminary toxicology study of at least 90 days to select the chronic dose levels which meet the requirements of this section. A preliminary toxicology study of at least 90 days that has been completed previously may be submitted for this purpose.

(iv) The sponsor must submit the rationale for dose selection including supporting data from preliminary toxicity studies as a part of the study plan submission.

(b) *Study conduct.* (1) *Clinical procedures.* A veterinarian, as specified in § 772.113–1(e)(2), must ascertain and be responsible for the health status and care of all test animals during the study. A technical employee, as specified in § 772.113–1(c)(3)(ii), must be responsible for the daily observations and care of the test animals.

(i) *Observation of Animals.* (A) Each test animal must be identified by a specific identification number. The tester must account for all animals at the end of the study. The tester must establish and adhere to standard operating procedures for housing, feeding, handling, and care of test animals as specified in § 772.110–1. To further assure minimal loss of animals due to cannibalism or autolysis of tissue, technical employees, as specified above, must observe the test animals at least once every 12 hours throughout the test period. EPA may consider study to be unacceptable for purposes of satisfying a test rule requirement if losses in any test group exceed 5 percent.

(B) Technical employees must conduct routine clinical examinations on all test animals. Clinical examination must include weighing of each animal, at approximately the same time of day, at least once a week during the first 13 weeks, and every two weeks thereafter and observing all animals in relation to food and water consumption, morbidity, mortality and causes thereof, loss of animals for whatever reason, signs of toxicity, pharmacologic effects, and behavioral changes. The observer must record all data in detail at the time of observation.

(ii) *Clinical laboratory testing.* The tester must conduct the following quantitative determinations on a minimum of eight additional predesignated rats in each test group. For nonrodents, all animals in each test group must be utilized. In addition to the tests listed below, if any interim clinical observations suggest that other tests are necessary to assess the health status of test animals, the appropriate tests must be conducted.

Note.—Predesignated means that the animal has been selected to undergo these tests by a specified randomization procedure prior to initiation of the study.

(A) *Hematology.* The tester must conduct the following quantitative hematologic determinations at least at 3, 6, 12, 18, 24 months and at study termination: hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts, platelet count, and prothrombin and clotting times. If hematologic evidence of anemia is present, reticulocyte counts must be performed within one week of the determination.

(B) *Blood chemistry.* The tester must conduct the following quantitative blood chemistry determinations at least at 3, 6, 12, 18, 24 months and at study termination: calcium, sodium,

potassium, chloride, serum lactic dehydrogenase, serum glutamic pyruvic transaminase, creatinine kinase, serum glutamic oxaloacetic transaminase, glucose, blood urea nitrogen, creatinine, direct and total bilirubin, cholinesterase, total cholesterol, triglycerides, serum alkaline phosphatase, albumin, globulin, and total protein. In addition to these tests, the tester may conduct other quantitative blood chemistry determinations at his/her discretion, such as uric acid, gammaglutamyl transpeptidase, and ornithine carbamoyltransferase.

(C) *Urinalysis.* The tester must conduct the following quantitative determinations at least at 3, 6, 12, 18, 24 months and at study termination: specific gravity or osmolarity, pH, protein, glucose, ketones, bilirubin, and urobilinogen, as well as microscopic examination and analysis of formed elements. Each animal's urine must be evaluated individually.

Note.—Additional Tests. Based on results of concurrent or previous studies on the test substance, its metabolic or degradation products, the tester should conduct such other determinations as may be necessary for adequate toxicological evaluation.

(D) *Function tests.* (1) The tester must determine the functional capacity of the renal, hepatic, pulmonary, and cardiovascular systems.

Note.—Additional determinations must place major emphasis on organ or system function tests. Selection of the appropriate tests must be based on the findings in the subchronic studies or observations made during the course of present study.

(2) Additional quantitative determinations may include, but not necessarily be limited to the following: water dilution and water concentration tests for renal function; total lung capacity, functional residual capacity, and residual volume for pulmonary function; bromsulphalein excretion test for liver function; electrocardiogram, blood pressure, and exercise recovery for cardiovascular function. The tester must perform these evaluations at the beginning (nonrodent only) and at least every 3, 6, 12, 18, 24 months and at study termination.

(E) *Residue analysis.* The tester must measure levels of test substance, major metabolites or other biologically significant metabolites at 3, 6, 12, 18, and 24 months ± 1 month and at the termination of the study. Tissues analyzed should include all subchronic target tissues and those suggested by pharmaco-kinetic studies. These analyses must include at least plasma, 24-hour urine, feces and, at time of death or scheduled killing, liver and kidney.

(iii) *Interim kill.* The tester may kill predesignated animals (other than those predesignated for hematological tests in paragraph (b)(1)(ii)(A) of this section) at any time during the study, provided that he/she increases the number of animals started in the study at least by the number scheduled or anticipated to be killed before the end of the study.

(iv) *Killing of test animals.* Animals which appear during the study as moribund, injured, or weak, and not expected to survive to the next observation, must be killed to preclude the loss of tissues from cannibalism and/or autolysis. Animals surviving to the termination of the study must also be killed. A technical employee must obtain blood samples for hematologic determinations from each animal immediately before it is killed or as it is killed. The method used for killing must be humane and the same throughout the study. The tester must select a method of killing which will not produce interfering pathologic lesions.

(2) *Pathology procedures.* A Board-Certified or Board-Eligible pathologist, as specified in § 772.113–1(e)(1)(i), must be responsible for the planning and conduct of all pathology procedures and histopathology examinations, as well as for the final interpretation of all pathology data. Other doctorate pathologists, as specified in § 772.113–1(e)(1)(ii), are also acceptable for conducting procedures in their disciplines of specialization, under the direct supervision of a Board-Certified or Board-Eligible pathologist as specified in § 772.113–1(e)(1)(i).

Note.—Direct supervision means that the supervisor is immediately available for consultation, as necessary. This consultation may be done in person or by telephone.

(i) *Gross necropsy.* (A) Qualified pathologists, as specified in § 772.113–1(e)(1), must perform or personally supervise the necropsies. Other appropriately trained technical employees, as specified in § 772.113–1(e)(3)(i) may assist in the necropsy.

Note.—Personal supervision means that the supervisor is immediately available for consultation at the site.

(B) Animals must be necropsied as soon as possible after death but no later than 16 hours after death. If necropsy cannot be performed immediately after the animal is killed, or found dead, a technical employee must immediately refrigerate (but not freeze) the animal at temperatures low enough to minimize tissue autolysis (4–6° C). Animals found dead upon routine clinical examination must be necropsied as soon as possible to salvage usable tissues.

(C) The gross necropsy must include an initial physical examination of the external surfaces and all orifices followed by an internal examination of tissues and organs *in situ.* The examination must include the following: external and internal portions of all hollow organs; cranial cavity and external surfaces of the brain and spinal cord; nasal cavity and paranasal sinuses; neck with its associated organs and tissues; thoracic, abdominal, and pelvic cavities with their associated organs and tissues; and the muscular/skeletal carcass. The urinary bladder and lungs must be inflated with a proper fixative to allow for better gross examination and preservation.

(D) The weights of the heart, liver, kidneys, testes, spleen, lung, brain, and adrenals must be recorded after careful dissection and trimming. In addition, the thyroid (with parathyroids) and pituitary must be weighed for each nonrodent. The person responsible for the gross necropsy must record all gross necropsy findings in accordance with § 772.113–1(k)(2).

(ii) *Tissue preservation.* A technical employee must immediately preserve all tissues and organs from all test animals in 10 percent buffered formalin or another recognized and accepted fixative appropriate for the specific tissue(s). Sections from the following tissues from all test animals regardless of their time of death must be properly preserved for routine microscopic examination.

(A) All gross lesions (with a margin of normal tissue);

(B) Brain (minimum of one section each from the forebrain, midbrain and hindbrain);

(C) Spinal cord (minimum of one section each from cervical, thoracic, and lumbar regions);

(D) Eyes and contiguous Harderian glands;

(E) Pituitary gland;

(F) Major salivary glands, thymus, thyroid with parathyroid, mammary glands, Zymbal's gland (if present);

(G) Oral mucous membrane (including random sections from tongue, buccal, and alveolar mucosa, pharynx, and nasopharynx);

(H) Heart and aorta (three sections from different locations);

(I) Trachea; lungs, with the mainstream bronchi;

(J) Esophagus, stomach, small intestines and large intestine (cecum, colon, and rectum);

(K) Adrenal glands, pancreas, liver (minimum of two lobes), gall bladder (if present), spleen;

(L) Kidneys, urinary bladder;

(M) Representative lymph nodes (including those draining any neoplasm and those with gross changes;

(N) Bone including marrow, from the sternum vertebra and/or tibiofemoral joint;

(O) Skin (sections from similar sites of all animals);

(P) Skeletal muscle;

(Q) for males: testes, prostate, and all other accessory organs;

(R) For females: vagina, corpus and cervix uteri, ovaries, and fallopian tubes.

(iii) *Preparation of tissue for microscopic examination.* A pathologist or a technical employee, as specified in § 772.113–1(e)(3)(i), must prepare all specimens for microscopic examination.

(A) *tissue fixation and trimming.* The technical employee must fix tissues for the appropriate times for the fixature utilized. A pathologist must perform or directly and personally supervise tissue trimming. Routinely, tissues must be trimmed to a thickness of no more than 0.4 cm for subsequent processing. Parenchymal organs must be trimmed to allow for the largest surface areas possible for subsequent microscopic examination. Hollow organs must be trimmed to allow for a cross section mount from mucosa to serosa. Lymph nodes must be bisected through the hilus, if possible.

(B) *Slide preparation.* A technical employee must cut tissues routinely at a thickness of three to six micra (3 to 6 μ), in no case exceeding 10 μ. All tissues must be stained routinely with hematoxylin and eosin (H&E). EPA encourages the use of special stains appropriate to the specific neoplasm, lesion, or tissue. Multiple sections (step cuts) must be made on each tissue or organ that contains gross evidence of a neoplasm or lesion and on each tissue or organ in which a metastasis may be anticipated. The tester must identify all blocks and microscopic slides by reference to the animal's specific identification number and must preserve and hold them in accordance with § 772.110–1(j)(2).

(iv) *Microscopic examination and evaluation.* (A) Qualified pathologists as described in § 772.113–1(e)(1), must perform the microscopic examination and evaluation with subsequent diagnosis. The same pathologist must examine and evaluate all microscopic slides from all test animals of a given species.

(B) Microscopic examination must be performed on all appropriate tissues described in paragraphs (b)(2)(ii), (b)(2)(v), and (b)(2)(vi) of this section. The pathologist must record, document, and report all microscopic findings including all abnormalities, lesions, neoplasms, metastatic tumors and their anatomic location in accordance with § 772.113–1 (k)(2).

(v) *Additional examinations.* All adverse health effects observed during the course of the study must be examined. When there is clinical evidence of specific toxicologic or pharmacologic effects related to specific target organs, the necropsy and microscopic examinations of the suspected target organs must be conducted in greater detail. For example, when there is clinical evidence of neurologic effects, multiple sections from brain, spinal cord, and nerves must be examined.

(vi) *Special examinations.* (A) Additional sections must be microscopically examined from a minimum of ten rodent animals selected randomly from the long-term survivors and all nonrodent animals of each test group and in all animals in which clinical or grossly observable evidence of disease is present. If microscopic examination reveals evidence of disease in any of these tissues, then these target tissues must be examined in all test animals.

(B) The necropsy and microscopic examination must include, in addition to those tissues listed in paragraph (b)(2)(ii) of this section, the following:

(*1*) *In a feeding study:* nasal cavity; paranasal sinuses; nasopharynx.

(*2*) *In an inhalation study:* multiple sections of the upper respiratory tract; nares; nasal cavity; paranasal sinuses; hypopharynx-larynx.

(*3*) *In a dermal study:* skin (normal); skin from sites of skin painting.

[FRL 1079–6; OTS–046003]
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[40 CFR Part 772]

Good Laboratory Practice Standards for Health Effects

AGENCY: Environmental Protection Agency.

ACTION: Proposed rule and notice of public meetings.

SUMMARY: This action proposes good laboratory practice standards for the development of data on the health effects of chemical substances and mixtures tested in accordance with testing rules promulgated under section 4 of the Toxic Substances Control Act (TSCA) (Pub. L. 94–469, 90 Stat. 2003, 15 U.S.C., 2601 *et seq.).*

When these proposed good laboratory practice standards are made final, they will be incorporated, as appropriate, into the testing rules on the chemicals for which EPA makes the findings required by Section 4 of TSCA. Compliance with these standards is intended to assure the reliability and adequacy of the submitted data.

The good laboratory practice standards include general standards that apply to all laboratory health effects testing under Section 4 of TSCA.

DATES: Interested persons are invited to submit written comments to EPA on these proposed standards prior to the close of business on August 7, 1979. See also Section VII, public participation, for further information.

PUBLIC MEETINGS: EPA has scheduled public meetings on these proposed standards. These meetings will be held during the week of July 9 in Chicago and during the week of July 16 in Washington, D.C. Additional information on these meetings including dates, times and locations, is presented in Section X, Public Meetings.

ADDRESSES: Written comments should bear the document control number OTS–046002 and should be submitted to: Ms. Joyce A. Barbour, Chemical Information Division, Office of Toxic Substances (TS–793), U.S. Environmental Protection Agency, 401 M Street SW, Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: Industry Assistance Office, Office of Toxic Substances (TS–799), Environmental Protection Agency, 401 M Street SW., Washington, D.C. 20460, Telephone No.: 800–424–9065 (toll-free); (In Washington, D.C., call 554–1404).

SUPPLEMENTARY INFORMATION: Following is an index to the remainder of this preamble:

I. Introduction.
II. Problem of unreliable test data.
III. EPA's approach to good laboratory practice.
IV. Proposed good laboratory practice standards
a. General—Scope, Purpose and Definitions,
b. Test and Control Substances and Mixtures,
c. Personnel and Organization,
d. Facilities,
e. Equipment,
f. Testing Facilities Operation,
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I. Introduction

Under Section 4(b) of TSCA (90 Stat. 2003, *et seq.* 15 U.S.C., 2601 *et seq.*, EPA is initiating its proposals for standards for the development of test data that are relevant to the determination that particular chemicals present, or do not present, an unreasonable risk to health. The proposal consists of this notice and a separate one entitled "Health Effects Test Standards for Toxic Substances Control Act Test Rules" (hereafter "Health Effects Test Standards") also appearing in today's **Federal Register.**

In this notice, EPA is proposing general Good Laboratory Practice (GLP) Standards for Health Effects. These GLP Standards are designed to assure the reliability and adequacy of data submitted. These practices are proposed to apply generally to all animal bioassay laboratory health effects studies conducted under Section 4 of TSCA by or on behalf of manufacturers or processors of chemical substances or mixtures.

The separate "Health Effects Test Standards" notice contains specific standards for long-term animal bioassays to test for oncogenic effects and other (non-oncogenic) chronic effects. The preamble to the Health Effects Tests Standards notice also contains a detailed discussion of the statutory and regulatory framework of Section 4 of TSCA. That discussion is incorporated in this notice by reference.

While these GLP Standards will apply generally, EPA will be proposing more specific regulations pertaining to the conduct of laboratory studies in test standards that relate to particular effects or in test rules pertaining to particular chemicals. For example, while these proposed GLP Standards state principles of general applicability relating to care of experimental animals and maintenance of laboratory equipment, the Oncogenic and Non-Oncogenic Chronic Effects Test Standards appearing in the "Health Effects Test Standards" notice deal with issues of specific laboratory practices and experimental design as they relate to chronic effects testing (see proposed § 772.113 of the "Health Effects Tests Standards").

These GLP Standards for Health Effects are proposed as generic standards for testing chemicals subject to rules under Section 4 of TSCA. In later rulemaking proceedings, EPA will identify chemicals to be tested. In the chemical specific rules, EPA intends to focus on the need to test the chemicals. For example, EPA will determine under Section 4 of TSCA that a chemical (1) may present an unreasonable risk of injury to health or the environment, or will cause significant environmental or human exposure; (2) that there are insufficient data to determine health or environmental effects of the chemical; and (3) that testing is necessary to develop the data. If a chemical meets these prerequisites, a testing rule will be developed that will incorporate, as appropriate, the GLP standards. Once the proposed GLP standards are finalized, EPA is not required to solicit further comment on the general GLP principles in the chemical specific rules. A more detailed explanation of the regulatory framework appears in the separate **Federal Register** notice on "Health Effects Tests Standards."

EPA intends, at a later date, to propose, as part of these general GLP Standards, specific criteria for other types of health effects testing such as *in vitro* biological studies. In addition, GLP Standards addressing chemical fate and ecological effects testing under TSCA will be proposed at a later date.

EPA is also considering whether these general GLP Standards should be used to provide guidance to persons making submissions to EPA under Section 5 of TSCA. EPA specifically invites comment on the issue of the applicability of these GLP Standards to Section 5 or any other Agency regulatory authority under TSCA.

II. The Problem of Unreliable Test Data

It is apparent that EPA will be evaluating substantial amounts of laboratory data under the authority of Section 4 of TSCA. It has been well documented that government agencies have faced the problem that submitted data may be unreliable or unusable for regulatory purposes. In assessing the need for GLP Standards under TSCA, EPA has drawn heavily on its own experience and that of the U.S. Food and Drug Administration (FDA).

In testimony before both the U.S. Senate Subcommittee on Health (Committee on Labor and Public Welfare) and the U.S. Senate Subcommittee on Administrative Practice and Procedure (Committee on the Judiciary), the Commissioner of the FDA raised questions concerning the integrity of data submitted to FDA in support of the safety of regulated products (7/10/75, 1/20/76, 4/8/76, and 7/19/76). Inspections by FDA of several pharmaceutical houses and contract laboratories led to the discovery of unacceptable laboratory practices that, in turn, called into question the validity of the test data submitted by those sources. The unacceptable practices noted included selective reporting and underreporting of test results, lack of adherence to specified protocols, inadequate qualification and supervision of personnel, poor animal care procedures, poor record-keeping techniques, and the general failure of sponsors to monitor studies. As a result of these findings, FDA proposed Regulations for Good Laboratory Practice (41 FR 51206, November 19, 1976) and published final regulations on December 22, 1978 (43 FR 59986).

Aware of FDA's findings, EPA responded to the problem of questionable data by forming the Toxicology Data Auditing Program within the Agency's Office of Pesticide Programs (OPP). This effort was directed toward toxicity data submitted under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (7 U.S.C. 136 *et seq.*).

Public hearings to invite comment on the appropriateness of the Agency's approach to data quality assurance for pesticide testing were held in October and November of 1977, in San Francisco, Chicago, and Washington, D.C. Public comment indicated the necessity for such a program and a general concurrence with the Agency's approach.

In March 1978, EPA entered into an Interagency Agreement with FDA that formalized the Agencies' cooperative efforts to establish a coordinated quality assurance program for their various activities (43 FR 14124, April 4, 1978). Under the terms of this agreement, FDA provides inspectional support for EPA's data audits. Since the cooperative program became fully operational, approximately 65 joint audits have been performed. Top priority for auditing has been given to testing facilities that generate chronic toxicity, oncogenicity, teratogenicity, reproduction, and neurotoxicity data in support of petitions for pesticide residue tolerances. In addition, several audits have been done "for cause"—namely, data inconsistencies or purported questionable practices brought to the program management's attention from sources both within and outside the Agency. As a result of this program, the Pesticides and Toxic Substances Enforcement Division (PTSED) of EPA has referred some audited facilities to the Department of Justice for possible

prosecution. Thus, the audits conducted to date, and the results reported, appear to indicate that testing facilities do not always follow good laboratory practices.

The cooperative efforts of EPA and FDA have been further expanded under a new Interagency Agreement that includes coordinated quality assurance activities for both FIFRA and TSCA.

III. EPA's Approach to Good Laboratory Practice

TSCA authorizes EPA to prescribe such standards as are necessary to assure test data are "reliable and adequate" (See Sections 3(12) and 4(b) of TSCA). To this end, EPA has considered various approaches to assure the quality of submitted data: (1) licensing or certification of laboratories; (2) a voluntary standard-setting scheme promulgated and administered by the private sector; and (3) promulgation of good laboratory practice standards that regulate testing procedures.

A laboratory licensing or certification scheme has been considered for TSCA purposes. The Agency has considered certification schemes for laboratories engaged in air and water quality monitoring under the Safe Drinking Water Act, the Clean Air Act, and the Water Pollution Control Act. Although a certification system is feasible for these analytical facilities, it would not be practical for toxicology laboratories because of the diversity and range of testing capabilities in these facilities. In addition, the quality control procedures for toxicity testing are more complex than those for air and water analysis; therefore, submitted data must be evaluated on a case-by-case basis.

The Agency also has considered the concept of a voluntary standard-setting scheme developed and administered by the industrial community or by scientific societies. Although such private sector programs are recognized as being potentially effective in improving testing practices and are thus to be encouraged, all such schemes are by their nature unenforceable. While it is expected that most laboratories will follow GLP Standards, an enforceable set of standards will provide the incentive to ensure that all laboratories comply.

The good laboratory practice standards approach, then, appears to be the most effective way of handling a problem of such magnitude and seriousness, since it will establish an enforceable program but will not needlessly expend Agency resources on an impractical certification scheme.

IV. Proposed Good Laboratory Practice Test Standards

This proposal sets forth standards for test substance characteristics, including handling and storage; personnel qualifications; and internal laboratory Quality Assurance Unit; administrative and personnel facilities; equipment; testing facilities operation; study design and conduct; records and reports; and inspections of laboratory facilities. In addition, guidance is provided in Appendix A for handling potentially toxic substances, including radioactive materials; for animal care facilities; for administrative and personnel facilities; and for animal care and handling. When evaluating submitted data, EPA will give serious consideration to whether a laboratory complies with the Appendix A Guidelines.

These proposed GLP Standards have been harmonized as much as possible with the GLP regulations promulgated by FDA on December 22, 1978 (43 FR 59986). However, EPA's and FDA's basic approach to regulation of the conduct of a laboratory study differs somewhat. FDA has only general good laboratory practice regulations, which are the equivalent of the standards set forth in this notice. In addition to these general standards, EPA will promulgate more specific standards that relate to particular effects or in test rules pertaining to particular chemicals. As a result, any general requirements of proposed § 772.10–1 set forth in this notice may be qualified by specific standards in specific rules. This notice, therefore, reflects a set of general standards that is common to the needs of both agencies.

EPA's proposal for general GLP Standards also differs from FDA's GLP regulations n the following areas: (1) EPA adds to the definition of "raw data" (Subsection 772.110–1(a)(3)) correspondence relating to planning, conduct and interpretation of the study; (2) in all cases, EPA requires stability testing of the chemical to be tested before the laboratory bioassay is initiated; and (3) EPA requires laboratories to retain certain data longer. In addition, standards contain an Appendix A that provides additional guidance not specifically contained in FDA's regulations. All these differences will be discussed below. Unless differences are specifically noted, each section of the EPA proposed general GLP Standards is substantially the same as the counterpart section in the FDA regulations. Note, however, that EPA does not propose a provision on "Disqualification of Testing Facilities," Subpart K of FDA regulations (43 FR 60019).

The preamble to the FDA rules contains 253 separate sections that provide detailed justification for the provisions of those rules. Many sections are also applicable to EPA's proposed GLP standards. These sections will be referenced, as appropriate, in subsequent sections of this preamble, as "FDA/GLP preamble section numbers. * * * " EPA invites comment on all issues presented in its proposed GLP Standards, whether or not the isues have been addressed by FDA.

Note further that since FDA's preamble is applicable only to the general standards proposed in this notice, FDA's preamble does not apply to specific effects testing standards in which EPA may provide more detail than in the general GLP rule. This situation is illustrated by comparing statements in FDA's/GLP preamble sections to EPA's proposed "Health Effects Test Standards" for chronic effects, which appears elsewhere in today's **Federal Register**. The FDA/GLP preamble notes that in FDA's regulations certain issues are left to the discretion of the testing laboratory or are beyond the scope of the regulations. These issues relate to the following areas: the appropriateness of the test system, determination of the adequacy of each standard operating procedure, contaminant analysis of feed, nutrient analysis, and expiration dates for feed (see FDA/GLP preamble section numbers 66, 135, 164, 165, 166, respectively, at 43 FR 59995–60008). EPA, on the other hand, delineates in the "Health Effects Test Standards" as they relate to chronic effects testing more specific requirements in each of these areas, as well as more detailed standards for study design and conduct, and reporting (see the "Health Effects Test Standards" § 772.113). For example, the FDA/GLP preamble section number 66 states that the "determination of the appropriateness of the test system is a scientific decision beyond the scope of these regulations" (43 FR 59995). In contrast, EPA proposes to require that for oncogenic effects test standards the use of two rodent species—the laboratory mouse and rat (§ 772.113-2(a)(1))—and that for non-oncogenic chronic effects test standards, a laboratory rat and a nonrodent mammalian species must be used (§ 772.113-3(a)(1)). Also, where FDA declines to provide specific guidance on nutrient analysis (FDA/GLP preamble section number 165), EPA provides detailed requirements for the rodent standardized diet in Appendix A of

§ 772.113 of its chronic health effects standards.

a. *General—Scope, Purpose, and Definitions—772.110–1(a).* EPA's definitions generally conform to FDA's, except with respect to those that relate to the differing scope of the authority of each agency. For example, EPA does not need to define "Application for research or marketing permit" (21 CFR 58.3(e); 43 FR 60014) and EPA's and FDA's definitions relating to "sponsor" of a study differ because of the differing authorities under which each agency regulates. (Compare 21 CFR 58.3(f) at 43 FR 60014, and EPA's proposed 772.110–1(a)(3)). Therefore, many of the sections in the "Definition" part of the preamble to FDA's regulations (FDA/GLP preamble section numbers 17–36) do not apply to EPA's standards. The following sections do apply generally to EPA's regulations: FDA/GLP preamble section numbers 17, 30–37, 43 FR 59990–92.

EPA has added to FDA's definition of "raw data" correspondence relating to the planning, conduct, and interpretation of the study. This issue has arisen as a result of recent FDA laboratory audits in which interpretations of data in lab records were found to be inconsistent with those in reports. FDA has not, as yet, formally addressed this issue, but it has supported this general approach in informal discussions.

b. *Test and Control Substances and Mixtures—772.110–1(b).* For a more detailed discussion of the issues relating to this section, see FDA/GLP preamble section numbers 168–192, 43 FR 60005–07. Paramount in any toxicology study is the assurance that the test system is properly exposed to the chemical substance being tested. In order to provide this assurance, EPA proposes specific quality assurance standards for test and control substances in this section. These proposed standards relate to the identity, purity, and composition of each batch of the test or control substance and to potential deterioration of the chemical substance during the period of administration.

This section also specifies that procedures be established for proper storage and handling of test and control substances. Standards relate to proper identification and documentation of receipt and distribution of these chemical substances.

Finally, this section addresses mixtures of test or control substances with carriers. Standards relate to determination of uniformity, concentration, and stability of the test or control substance in the mixture.

Proposed § 772.110–1(b) generally conforms to Subpart F of FDA's GLP regulations (43 FR 60017–18). The major difference between proposed EPA and FDA final GLP regulations is that EPA proposes to require that the stablility of a test substance or mixture (including shelf life stability and stability in feeds and/or vehicles) must, in all cases, be established before the initiation of any study while FDA permits concurremt stability testing. Also, EPA requires that each batch of an unstable test substance or mixture must be analyzed before the batch is used in the study. Compare EPA proposed §§ 772.110–1(b)(1)(ii); 772.110–1(b)(3)(i)(B); and 21 CFR sections 58.105(b), 58.113 at 43 FR 60017–18; FDA/GLP Preamble, section numbers 174, 188, 195 at 43 FR 60007. Both agencies still emphasize that determination of stability is an important requirement, but only differ as to timing of the stability determinations.

EPA believes that its proposal on stability testing represents sound laboratory practice. Stability studies are generally of short duration and will not significantly delay the toxicologic evaluation. For example, if a chronic study were to be initiated or even completed before the stability kinetics of the test substance were established and the tested substance was later found to be unstable, the study might have to be repeated, with considerable duplication of effort and delay resulting. For TSCA regulatory purposes, such a delay is considered unacceptable.

c. *Personnel and Organization—772.110–1(c).* For a more detailed discussion of the issues relating to this section, see FDA/GLP preamble section numbers 50–93, 43 FR 59994–99. The Agency considers adequate training and experience to be key factors in assuring the quality of the data generated. The proposed standard also defines responsibilities for the management of the testing facility, the Study Director, and the laboratory Quality Assurance Unit. The testing facility management is responsible for designating the Study Director, for the existence of a Quality Assurance Unit, and, in general, for assuring that any deviations from these Standards are appropriately reported, documented, and corrected.

A major difference between EPA's and FDA's approach to personnel qualifications is that EPA also will propose more specific requirements in Standards relating to testing of specific effects. In the proposed "Health Effects Test Standards," appearing elsewhere in this **Federal Register**, EPA proposes specific qualifications for personnel conducting chronic effects studies (772.113–1(b)(2)). FDA has no such counterpart in its regulations and rejects such specific requirements (see FDA/GLP preamble section number 49, 43 FR 59994). EPA requests comment on the requirements it proposes to impose on persons conducting studies for use by EPA. EPA notes that since these qualifications are testing standards under Section 4 of TSCA, any laboratory that violates the Standards could be held in violation of EPA regulations, or may run the risk of having its data rejected by EPA (See § 770.5, in the "Health Effects Test Standards" notice appearing elsewhere in this **Federal Register**).

(1) *Study Director.* Before the initiation of a study, the proposal requires that a Study Director be identified and assume ultimate responsibility for the implementation and conduct of the study. Experience has shown that unless responsibility for the proper conduct of a study is assigned to one person, there is potential for conflicting instructions and poor protocol implementation. The Study Director would be responsible for assuring that: the sponsor-approved protocol is followed; test systems are appropriate for the study; personnel involved in the study clearly understand their functions and are qualified to perform them; data are accurately and promptly verified and recorded; health hazards to the test system that appear during the study are recognized and removed; quality assurance procedures are followed; the studies are conducted in a manner that is safe for laboratory personnel; and the required data have been transmitted to the archives for storage.

(2) *Quality Assurance Unit.* In order to assure that quality control procedures are followed, the proposed standards require that testing facility management establish an internal Quality Assurance Unit that will provide an effective mechanism for monitoring ongoing studies.

Both EPA's proposed GLP Standards and the FDA final regulations exclude from GLP inspections Quality Assurance Unit records of findings and problems, or actions recommended and taken (See EPA's proposed § 772.110–1(k); see FDA's final regulation, 21 CFR 58.15 at 43 FR 60015; 21 CFR 58.35(c) at 43 CFR 60016; FDA/GLP preamble section number 91 at 43 FR 59998). EPA, however, is considering whether to subject such records to routine inspection procedures, since inspection of these files would provide the Agency with additional information regarding follow-up procedures and the corrective measures taken by the testing facility management in dealing with problems

associated with the management of the quality assurance unit and the studies it oversees. This type of information may be of considerable value for enforcement purposes. EPA specifically invites comment as to whether all quality assurance unit records, including records of findings and problems, or action recommended and taken, should be subject to routine inspection.

d. *Facilities—772.110–1(d).* For additional discussion of this section, see FDA/GLP preamble section numbers 94–112, 43 FR 59999–60000. This section of the proposal addresses standards relating to animal facilities, animal supply facilities, facilities for handling test and control substances, laboratory operation areas, specimen and data storage facilities, and administrative and personnel facilities.

EPA differs from FDA in that EPA's GLP Standards contain the following additional guidance in Appendix A:

(1) EPA proposes guidance with regard to structural requirements and environmental control of animal facilities. These conditions may impact the validity of the data generated. As such, specific reference to the Animal Welfare Act is included in the Guidelines provided in Appendix A of this subsection.

(2) EPA proposes specialized guidelines for the handling of volatile agents, hazardous aerosols, radioactive materials, and other potentially toxic substances. Specific reference is made in Appendix A to (1) the Nuclear Regulatory Commission's regulations as set forth in 10 CFR, (2) to the Department of Health, Education and Welfare draft document entitled, "Guidelines for the Laboratory Use of Toxic Substances Posing an Occupational Carcinogenic Risk" (August 1978), and (3) to the International Agency for Research on Cancer document entitled, "A Manual on the Safety of Handling Carcinogens in the Laboratory."

(3) Guidelines for Administrative and Personnel Facilities are also provided in Appendix A. Specific reference is made to OSHA regulations set forth in Title 29 of the CFR.

(4) Guidelines are provided for Animal Care and Handling. EPA is of the opinion that the standards contained in the Federal gudelines and regulations cited in Appendix A and any revisions in them are sufficient to assure the quality of the data generated by a facility; therefore, the Agency has incorporated them by reference in this proposal.

e. *Equipment—772.110–1(e).* For further detailed discussion of the issues involved in this section see FDA/GLP preamble section numbers 113–129, 43 FR 60000–01.

This section proposes that laboratories established standards relating to equipment design, maintenance, and calibration and standard operating procedures for routine equipment inspection and standardization. In addition, proposed requirements are specified for the maintenance of written records for all inspection, maintenance, testing, calibrating, and/or standardizing operations. Such records will serve to document the nature of the defect and any remedial action(s) taken.

f. *Testing facilities operation—772.110–1(f).* For detailed discussion of the issues involved in this section, see FDA/GLP preamble section numbers 130–167, 43 FR 60002–05.

(1) *Standard operating procedures.* In order to ensure the quality and integrity of study data, it is proposed that laboratories establish written standard operating procedures for such areas as transfer, proper placement, identification, and care of animals; receipt, storage, testing, mixing, and administration of the test and control substances; maintenance and calibration of equipment; test system observations; laboratory tests; handling of animals found dead or moribund during a study; necropsy or postmortem examination of animals; collection and identification of specimens; and data handling storage, and retrieval.

(2) *Animal care.* Proper care and handling of test animals are essential to the quality of the data generated. EPA is proposing standards for the isolation and quarantine of sick animals or all animals newly received from outside sources. Such quarantine is believed necessary to preclude transmission of disease to animals already in the facility.

EPA is also proposing standards for animal identification, housing, and environmental conditions. Documentation will be required for periodic feed and water analysis, as well as for the use of any pest control materials. In addition, the Agency believes that further guidance is necessary in the general area of animal handling and care. As such, specific reference is made in Appendix A to the Animal Welfare Act of 1970, as set forth in 9 CFR Part 3. There is no counterpart to Appendix A in FDA's regulations.

g. *Protocol for and Conduct of a Study—770.110–1(g).* For a detailed discussion of the issues involved in this section, see FDA/GLP preamble section numbers 193, 194, 196–208, 43 FR 60007–09.

(1) *Protocol.* A written, sponsor-approved protocol is essential to ensure that all operations needed to fulfill the stated objectives of a study are performed. Previous EPA audits have shown that unauthorized deviations from protocols have occurred during the management of some studies, compromising their quality and integrity. This proposed section requires that certain informational components of a protocol be specified and carefully followed.

(2) *Conduct of the study.* This proposed section addresses several problems that have been identified in the area of study management. Adherence to the sponsor-approved protocol and to Agency test standards is required. Requirements relating to specimen identification are included to minimize the assignment of specimens to the wrong test system. It is also proposed that records of postmortem observations be made available when a pathologist is examining a specimen microscopically. This will assist the pathologist in correctly describing the microscopic findings and correlating them with gross observations. EPA also proposes standards for data collection and recording, in order to minimize the loss or inaccuracy of data generated during the management of a study.

h. *Records and reports—772.110–1(j).* For a detailed discussion of the issues involved in this section, see FDA/GLP preamble section numbers 210–230, 43 FR 60009–10.

(1) *Reporting of study results.* It is proposed that the final report be a complete and accurate representation of actual laboratory experience. EPA intends to publish detailed formatting requirements for these reports in the near future. The Agency proposes in these generic GLP Standards to require that the sponsor include all pertinent results, observations, and conclusions related to a study and that it document fully and completely all the conditions and circumstances under which a study was conducted. This proposed section specifies the informational content of the final report. It proposes that the final report be signed and dated by the Study Director and that the report of each individual scientist or other professional involved in the study be signed and dated by that responsible person. It also proposes that corrections or additions to a final report be in the form of an amendment by the Study Director. Such an amendment must clearly identify that part of the final report that is being amended or corrected and must specify

the reasons for the corrections or additions and be signed and dated by the person responsible for such changes.

(2) *Storage and retrieval of records and data.* Proper storage and ready retrieval of the raw data associated with a study are vital for the reconstruction of that study at a later time. Accessibility to such properly preserved data is of paramount importance to the Agency's auditing effort. This subsection proposes to require that all raw data, documentation, protocols, specimens, and final reports generated in connection with a study be retained in an archive(s) under conditions of storage which minimize deterioration of such documents and specimens and assure their preservation in case of a catastrophic event. This subsection also proposes that an individual be identified or responsible for the archives and that materials retained be indexed by test substance or mixture, test system, data and nature of the study.

(3) *Retention of records.* The proposal would require that every attempt be made by the testing facility or sponsor to retain raw data associated with a study for as long as the study is utilized for regulatory purposes or as long as the quality permits evaluation. Practical limitations, however, dictate that minimum periods of retention be established by regulation. As such, the Agency proposes in this subsection that documentation, records, raw data, and specimens pertaining to a study be retained for a period of at least ten (10) years from the date the study is submitted to the Agency. For relatively unstable wet specimens, or materials, retention is required only as long as the quality of the preparation affords evaluation.

If a testing facility goes out of business, all raw data and other documentation shall be transferred to the archives of the sponsor of the study, and the Agency shall be notified in writing of such a transfer and its specific location. If a facility conducting testing changes ownership or management, the Agency and the Sponsor must be notified and concur with the disposition of the archives.

Storage conditions for temperature sensitive specimens are stressed in this proposed section. Wet tissues, paraffin blocks, and other such specimens are to be stored under conditions which will promote their integrity and usefulness for the required retention period. It is recognized that certain types of specimens do not remain stable and of evaluative quality during storage; therefore, these types will be expected to be retained only as long as the quality of the preparation affords evaluation.

The Agency proposal differs with FDA with regard to the length of the required raw data and specimen retention period. See FDA/GLP preamble section numbers 225–226, 43 FR 60009–10. Since the EPA may wish to perform a data audit at any time during the marketing life of a chemical, a ten (10) year retention requirement is proposed. EPA will also consider comments relative to longer periods for retention of raw data.

i. *Inspection of testing facilities—772.110–1(k).* In order to assure that data development for the Agency is reliable and accurate, EPA believes that Agency personnel or agents must have the opportunity to inspect on a periodic basis the facility that conducts testing under Section 4 and to inspect (and in the case of records, to copy) *all* records and specimens required to be maintained. Although inspections on health effects studies will generally be conducted for EPA by FDA inspectors, EPA will pursue enforcement action regardless of the source of information. Any inspection will be conducted at reasonable times and in a reasonable manner, and under procedures to avoid inconvenience or intrusion into the work conducted by the inspected laboratory. Inspections, however, should be performed unannounced in order to insure the integrity of the inspection process. EPA expects that facilities generally will voluntarily permit entry of inspectors. In those circumstances in which facilities refuse entry the rules provide three consequences, explained below. The consequences considered by EPA are based on theories that do not precisely correspond with the theories that support the inspection authority of FDA because of the different statutory authorities under which each agency operates. See FDA/GLP preamble section numbers 39–48, 43 FR 59993–94. In addition, since EPA will promulgate more specific GLP Standards in chemical testing rules, EPA's inspections will in some instances be conducted with a greater level of detail. However, inspectors will be directed only toward tests being conducted under the requirements of TSCA.

Under proposed § 772.110–1(k)(1), EPA may take appropriate enforcement action against any laboratory (including an independent testing facility) that denies EPA entry for inspection purposes. The authority for this rule derives from Section 4(b)(1) of TSCA which directs EPA to promulgate "standards for development of test data." These standards are defined in Section 3(12)(B) of TSCA to include those requirements necessary to assure that data developed under testing rules are reliable and adequate, and "such other requirements as are necessary to provide such assurance." The Agency feels that lab inspections are necessary to provide this assurance.

Under proposed § 770.5 of the "Health Effects Tests Standards" appearing separately in this edition of the **Federal Register**, EPA will consider in violation of the Act data submitted by a facility that has not permitted EPA to inspect. The sponsor and/or other person conducting the test may then be liable under the Act for submitting data not in compliance with the rule. The Agency expects that such authority would be used, for example, when the Agency has received data, which it is not able to evaluate under scientific criteria accepted by the Agency.

Finally, by the terms of proposed § 772.110-1(k)(2), EPA will not consider reliable for purposes of indicating that a chemical does not present an adverse environmental or health effect any study performed by a laboratory that refuses entry. This action is separate from any enforcement authority held by the Agency, and derives from the presumption that EPA cannot be assured that the study conducted by a facility that has refused entry has been developed in accordance with the applicable standards. In such circumstances, it is within the Agency's discretion to question the validity of the study. EPA would simply be exercising its responsibility to consider a factor relevant to the weight to be given a study in the evaluation of a chemical. The Agency may, at its discretion, rely for purposes of showing a chemical causes adverse effect upon a study conducted by a laboratory that does not consent to inspections.

The Agency requests comments on these compliance measures. EPA will consider comments on other possible methods which it might adopt or on the advisability of including some or all of the alternatives in the final rule, including comments upon EPA's authority under TSCA to adopt any or all of these compliance measures. Comments are also welcome on the procedures the Agency should use to ensure that laboratory facilities permit entry for inspection purposes and that such entry is made in the least disruptive fashion consistent with EPA's need to assure the reliability of test data.

V. Confidentiality

EPA notes that trade secrets obtained as a result of GLP inspection conducted under these regulations are protected under the provisions of Section 14 of TSCA (15 U.S.C. Section 2613) and 40 CFR, Part 2 (as amended, 43 FR 39997, September 8, 1978). Basically, this means that EPA will not disclose confidential information to the public except in very limited circumstances. Furthermore, EPA will not disclose information claimed to be confidential without prior notice to the submitter, even if EPA believes the information is not confidential.

Subsection 14(b) of TSCA provides that EPA may not withhold from public disclosure, "any health and safety study which is submitted under this Act with respect to * * * any chemical substance or mixture for which testing is required under Section 4 [of TSCA], * * *" although Section 14(b) does not authorize release of any data which disclose processes used in chemical manufacturing or processing or the portions of a mixture comprised by any chemical substance.

EPA recognizes that a person performing a GLP inspection may require access to information which the sponsor or laboratory may consider to be confidential. If such information has not yet been formally submitted to EPA, or previously requested by EPA under any other authorities of TSCA, the Agency believes that such information is not subject to public disclosure under Section 14(b) of TSCA.

EPA reserves the right to determine whether information claimed to be confidential is in fact entitled to confidential treatment under 4 CFR, Part 2 and also notes that pursuant to Section 14(a) of TSCA confidential information may still be disclosed to the public if necessary to protect health or the environment against unreasonable risk of injury or where relevant in any proceeding under TSCA.

EPA invites comment on its interpretation of Section 14(b). The Agency will also consider comments that Section 14(b) requires greater disclosure than stated in the interpretation.

VI. Economic Analysis

In December 1977, FDA estimated that the total estimated annual costs for domestic, non-governmental laboratories to comply with FDA's GLP regulations (on which EPA patterned its won GLP standards) would be $32.6 million. The costs of compliance with EPA's GLP requirements will be determined by the specifics of EPA regulatory programs and the extent to which laboratories have already incurred costs to comply with FDA GLP's. EPA and FDA have been jointly developing GLP regulations to minimize the joint cost of compliance.

EPA believes that additional costs that may be attributed to its GLP Standards are justified, since the Standards are necessary to assure adequate and reliable data for use in determining whether a chemical will present unreasonable risks to health. lesser standards, as experience shows, could result in a significant reduction in quality of data and serious detriment to the risk assessment process.

VII. Public Participation

During the development of these proposed regulations, a public meeting, was held on August 15, 1978, for which an announcement appeared in the Federal Register (43 FR 34841; August 7, 1978). In addition, drafts of these standards were discussed with the EPA's Science Advisory Board on June 22 and August 18, 1978. These meetings were also open to the public and announced in the Federal Register (43 FR 23013, May 30, 1978; 43 FR 32185, July 25, 1978). The Science Advisory Board also solicited public viewpoints to contribute to its critique of drafts of proposed standards.

VIII. Other Quality Assurance Issues of Concern to the Agency

a. *Ecological effects and chemical fate data.* Although this proposed regulation pertains to health effects data, the Agency must also concern itself with the quality of other types of data required under TSCA. The Agency is currently drafting good laboratory practice standards for the conduct of studies for ecological effects and Chemical Fate testing, and is developing strategy for implementing an inspection/audit program involving other governmental institutions which perform these types of tests. Concurrently, EPA is also developing a training program for its own regional enforcement personnel in order to prepare them for their roles in the OTS Quality Assurance Program.

b. *Agency-wide quality assurance effort.* Health and ecological effects as well as monitoring data are filed with the Agency pursuant to several Acts administered by other Offices within EPA. These Acts include, but are not limited to, the Safe Drinking Water Act, the Clean Air Act, the Resource Conservation and Reclamation Act, and the Water Pollution Control Act. The Offices which administer these mandates have similar concerns regarding the quality of the data submitted pursuant to these Acts. In order to present unified input to inter-Agency and international levels of organization dealing with quality assurance issues, the Office of Toxic Substances will participate in the coordination of the various quality assurance programs within other offices of the Agency.

c. *International implications.* Since much of the data utilized by EPA for regulatory decision making is generated in countries outside the United States, the Agency considers international coordination of quality assurance issues to be of prime importance for the effectiveness of its Program. The Administrator believes that all data utilized by the Agency should be judged by the same standards of quality. The Agency will work within the framework of the Organization of Economic Cooperation and Development (OECD) to carry out this policy.

IX. Legal Basis

These standards are being proposed as mandatory requirements under Sections 3(12)(B) and 4(b)(1)(B) of TSCA.

Section 3(12)(B) of TSCA defines the terms "standards for the development of test data" to include setting of requirements:

> To the extent necessary to assure that data respecting such effects and characteristics (relating to the health and environmental consequences of exposure to a particular chemical) are reliable and adequate—
>
> (i) The manner in which such data are to be developed,
>
> (ii) The specification of any test protocol or methodology to be employed in the development of such data, and
>
> (iii) Such other requirements as are necessary to provide such assurance.

Specific authority for adoption of such standards is found in Section 4(b)(1)(B) of TSCA, which specifies that rules adopted pursuant to Section 4(a) shall contain such "standards for the development of test data * * *."

X. Public Meetings

EPA will hold public meetings during the comment period to provide the public an opportunity to present comments and questions.

The Agency plans to hold three public meetings on these proposed standards during the week of July 9 in Chicago and during the week of July 16 in Washington, D.C. The purpose of these meetings is to enable interested persons to provide oral comments on the proposed rulemaking to EPA officials who are directly responsible for

developing the standards and supporting provisions of the rule.

Persons who wish to present their comments at any one of the meetings should contact EPA no later than four days before the meeting date by calling toll-free at 800–424–9065 (in Washington, D.C., call 554–1404), or by writing to the address listed at the beginning of this preamble under "For Further Information Contact."

Presenters are urged, but not required, to submit copies of their statements on the day of the meeting. All such written materials will become a part of EPA's record for this rulemaking. In addition to these written materials, the Agency will include the written transcripts of the public meetings in the public record.

Note.— These are the same meetings at which EPA will receive oral comments on the "Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules," notice of which appears elsewhere in today's **Federal Register**.

XI. Public Record

EPA has established a public record for this rulemaking (docket number OTS 046003) which is available for inspection in the OTS Reading Room from 9:00 a.m. to 5:00 p.m. on working days (Room 710E, 401 M Street, S.W., Washington, D.C. 20460). This record includes basic information considered by the Agency in developing this proposal. The Agency will supplement the record with additional information as it is received. The record includes the following categories of information:

(1) U.S. EPA–OTS. "Good Laboratory Practice Standards for Health Effects."

(2) U.S. EPA–OTS, "Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules": Support Document

(3) Working drafts of the proposed rules and the preamble which were available for public comment.

(4) Correspondence between EPA personnel and persons outside the Agency pertaining to development of the standards and preamble. (This does not include inter- or intra-agency correspondence, unless specifically noted on the index of the rulemaking record).

(5) Minutes, summaries, or transcripts relating to public meetings held to develop the standards.

All publicly available published documents, including FDA's GLP Preamble (43 FR 59986), cited in this preamble are incorporated by reference in the rulemaking record. EPA also incorporates by reference and takes notice of the public record in the FDA/GLP proceedings on FDA's GLP regulations, FDA Docket No. 76N–0400. EPA will also accept additional material for the record at any time between this proposal and the final designation of the rulemaking record. EPA will identify the complete rulemaking record on or before the date of promulgation of these regulations as prescribed by TSCA Section 19(a)(3).

Note.— Under Executive Order 12044, EPA is required to judge whether a regulation is "significant" and therefore subject to the procedural requirements of the Order or whether it may follow other specialized development procedures. EPA labels these other regulations "specialized." I have reviewed this regulation and determined that it is a specialized regulation not subject to the procedural requirements of Executive Order 12044.

Dated: April 27, 1979.

Douglas M. Costle,
Administrator, Environmental Protection Agency.

It is proposed to add Part 772, Subpart B, consisting at this time of § 772.110–1 which reads as follows:

PART 772—STANDARDS FOR DEVELOPMENT OF TEST DATA

Subpart B—Good Laboratory Practice Standards

Sec.

772.110–1 Good laboratory practice standards for health effects.
(a) General.
(1) Scope and purpose.
(2) applicability.
(i) General.
(ii) Studies performed under grants and contracts.
(3) Definitions.
(b) Test and control substances.
(1) Characterization.
(2) Handling.
(3) Mixtures of substances with carrier.
(c) Personnel and organization.
(1) Personnel.
(i) General requirements.
(ii) Specific requirements.
(2) Testing facility management.
(3) Study director.
(4) Quality Assurance Unit.
(d) Facilities.
(1) General.
(2) Animal care facilities.
(3) Animal supply facilities.
(4) Facilities for handling testing and control substances.
(5) Laboratory operation areas.
(6) Specimen and data storage facilities.
(7) Administrative and personnel facilities.
(e) Equipment.
(1) Equipment design.
(2) Maintenance and calibration of equipment.
(f) Testing facilities operation.
(1) Standard operating procedures.
(2) Reagents and solutions.
(3) Animal care.
(g) Protocol for and conduct of a study.
(1) Protocol.
(2) Conduct of a study.
(h)–(i) [Reserved]
(j) Records and reports.
(1) Reporting of study results.
(2) Storage and retrieval of records and data.
(3) Retention of records.
(k) Inspection of a testing facility.

Appendix A

(a) Handling of potentially toxic substances.
(b) Animal care facilities.
(c) Handling of radioactive materials.
(d) Administrative and personnel facilities.
(e) Animal care and handling.

Authority: Section 4, Toxic Substances Control Act (90 Stat. 2006, 15 U.S.C. 2603).

Subpart B—Good Laboratory Practice Standards

§ 772.110–1 Good laboratory practice standards for health effects.

(a) *General.* (1) *Scope and purpose.* This section prescribes good laboratory practice standards for conducting studies relating to health and safety evaluation. Compliance with this section is intended to assure the quality and integrity of health and safety data submitted pursuant to Section 4 of the Toxic Substances Control Act (TSCA) (Pub. L. 94–469, 90 Stat. 2003, 15 U.S.C. 2601 *et seq.*).

(2) *Applicability.* (i) *General.* The standards in this section apply to all health effects data developed and submitted to meet requirements of TSCA Section 4 test rules. In addition, more specific or detailed requirements are specified in specific test standards.

(ii) *Studies performed under grants and contracts.* When a sponsor utilizes the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service, it must notify the consulting laboratory, contractor, or grantee that the service is part of a study that must be conducted in compliance with the provisions of this part.

(3) *Definitions.* The definitions in Part 770 apply to this section. In addition, the following specific definitions apply to this section:

(i) "Test substance" means the specific form of a chemical substance or mixture that is used to develop data to meet the requirements of a TSCA Section 4(a) test rule.

(ii) "Control substance" means any chemical substance or mixture or other material that is administered to the test system in the course of a study for the purpose of establishing a basis for comparison with the test substance.

(iii) "Sponsor" means any manufacturer (including importer) or processor(s) of a chemical substance or

mixture for which testing is required under a TSCA test rule who conducts and/or causes to be conducted health and environmental effects tests required by TSCA test rules and/or submits data developed in accordance with the rule to EPA. "Sponsor" includes any manufacturer or processor who designates a second manufacturer or processor or a tester to develop such health and environmental effects data.

(iv) "Tester" means any person who develops health and/or environmental effects data to meet the requirements of a TSCA test rule, including any sponsor who develops such data and any independent consulting laboratory that develops such data.

(v) "Testing facility" means the persons, premises, and operational units that the tester uses or has used for the development of health and environmental effects data required by TSCA test rules.

(vi) "Person" means any natural person, firm, company, corporation, joint-venture, partnership, sole proprietorship, association, or any other business entity, any State or political subdivision thereof, any municipality, any interstate body and any department, agency, or instrumentality of the Federal government.

(vii) "Test system" means any animal, plant, micro-organism, or subparts thereof, to which the test or control substance or mixture is administered or added for study. "Test system" also includes appropriate groups or components of the sytem not treated with the test or control substance or mixture.

(viii) "Specimen" means any material derived from a test system for examination or analysis.

(ix) "Raw data" means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated and verified accurate by signature), the exact copy of exact transcript may be substituted for the original source as raw data. "Raw data" may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, recorded data from automated instruments, and correspondence relating to the planning, conduct, and interpretation of the study.

(x) "Quality assurance unit" means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of the studies.

(xi) "Study director" means individual responsible for the overall conduct of a study.

(xii) "Protocol" means a detailed description of the study and conduct to be followed.

(xiii) "Batch" means a specific quantity or lot of a test or control substance that has been characterized according to paragraph (b)(1)(i) of this section.

(xiv) "Impurity" means a chemical substance which is unintentionally present with another chemical substance.

(b) *Test and control substances.* (1) *Characterization.* (i) The identity, strength, purity, and composition or other characteristics which will appropriately identify the test or control substance must be determined for each batch and must be documented before the initiation of the study. Methods of synthesis, fabrication, or derivation of the test and control substances must be documented by the sponsor or the testing facility.

(ii) The stability of each test or control substance must be determined by the testing facility or by the sponsor before initiation of the study. If because of test or control substance instability, the stability of each batch of test or control substance to be used during the study cannot be determined before use of such batch, standard operating procedures must be established and followed to provide analysis of each batch.

(iii) Each storage container for a test or control substance must be labeled by name, chemical abstract number (CAS) or code number, batch number, expiration date, if any, and storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control substances. Storage containers must be assigned to a particular test substance for the duration of the study.

(iv) For studies longer than 4 weeks, reserve samples from each batch of test and control substances must be retained for the period of time provided by paragraph (j)(3)(i) of this section.

(2) *Handling.* Procedures must be established for a system for the handling of the test and control substances to ensure that:

(i) There is proper storage.

(ii) Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.

(iii) Proper identification is maintained throughout the distribution process.

(iv) The receipt and distribution of each batch is documented. Such documentation must include the date and quantity of each batch distributed or returned.

(v) In addition to the requirements set forth in paragraphs (b)(2)(i)–(iv) of this section, more detailed procedures for handling of potentially toxic substances are presented as guidelines in Appendix A of this section.

(3) *Mixtures of substances with carriers.* (i) For each test or control substance that is mixed with a carrier, tests by appropriate analytical methods must be conducted:

(A) To determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control substance in the mixture.

(B) To determine the stability of the test and control substances in the mixture. If because of test mixture instability, the stability of each batch of the test mixture cannot be determined before use of such batch, standard operating procedures must be established and followed to provide for periodic analysis of each batch.

(ii) For studies of more than 4 weeks' duration, a reserve sample of each test or control carrier substance mixture must be taken and retained for the period of time provided by paragraph (j)(3)(i) of this section.

(iii) Where any of the components of the test or control substance carrier mixture has an expiration date, that date must be clearly shown on the container. If more than one component has an expiration date, the earliest date must be shown. Storage requirements under paragraph (b)(1) of this section apply also to test or control substance/carrier mixtures.

(c) *Personnel and organization.* (1) *Personnel.* (i) *General requirements.* (A) Each individual engaged in the conduct of or responsible for the supervision of a study must have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions.

(B) Each testing facility must maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a study.

(C) There must be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

(D) Personnel must take necessary personel sanitation and health precautions designed to avoid

contamination of test and control substances and test systems.

(E) Personnel engaged in a study must wear clothing appropriate for the duties they perform. Such clothing must be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test and control substances.

(F) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the study must be excluded from direct contact with test systems, test and control substances, and any other operation or function that may adversely affect the study until the condition is corrected. All personnel must be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a study.

(ii) *Specific requirements.* In addition to the personnel requirements as described in paragraph (c)(1)(i) of this section, more specific personnel requirements will be specified in individual test standards.

(2) *Testing facility management.* For each study, testing facility management must:

(i) Designate a study director as described in paragraph (c)(3) of this section before the study is initiated.

(ii) Replace the study director promptly if it becomes necessary to do so during the conduct of a study, and document and maintain such action as raw data.

(iii) Assure that there is a quality assurance unit as described in paragraph (c)(4) of this section.

(iv) Assure that test and control substances or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity.

(v) Assure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled.

(vi) Assure that personnel clearly understand the functions they are to perform.

(vii) Assure that any deviations from these regulations reported by the quality assurance unit are documented and communicated to the study director and if corrective actions are required, they are taken and documented.

(3) *Study director.* For each study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, must be identified as the study director. The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation, and reporting of results, and represents the single point of study control. The study director must assure that:

(i) The protocol, including any change, is approved as provided by paragraph (g)(1) of this section and is followed.

(ii) All data, including observations of all responses of the test system, are accurately recorded and verified.

(iii) Unforeseen circumstances that may affect the quality and integrity of the study are documented when they occur, and corrective action is taken and documented.

(iv) Test systems are as specified in the protocol.

(v) All applicable good laboratory practice regulations are followed.

(vi) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

(4) *Quality assurance unit.* (i) A testing facility must have a quality assurance unit composed of one or more individuals who must be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this section. For any given study the quality assurance unit must be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

(ii) The quality assurance unit must:

(A) Maintain a copy of a master schedule sheet of all studies conducted at the testing facility indexed by test substance and containing, for each study, the test system, nature of study, date study was initiated, current status of each study, name of the sponsor, name of the study director, and status of the final report.

(B) Maintain copies of all protocols pertaining to all studies for which the unit is responsible.

(C) Inspect each phase of a study periodically and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. For studies lasting more than 6 months, inspections shall be conducted every 3 months. For studies lasting less than 6 months, inspections must be conducted at intervals adequate to assure the integrity of the study. Any significant problems which are likely to affect study integrity found during the course of an inspection must be brought to the attention of the study director and management immediately.

(D) Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.

(E) Determine that no deviations from sponsor approved protocols or standard operating procedures were made without proper authorization and documentation.

(F) Review the final study report to assure that such report acurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study.

(G) Prepare and sign a statement to be included with the final study report, which must specify the dates inspections were made and the dates findings were reported to management and to the study director.

(iii) The responsibilities and procedures applicable to the quality assurance unit, the records maintained by the quality assurance unit, and the method of indexing such records must be in writing and must be maintained. These items including inspection dates, the study inspected, the phase or segment of the study inspected, and the name of the individual performing the inspection must be made available for inspection to authorized employees of the Environmental Protection Agency or of the Food and Drug Administration.

(iv) A designated representative of the Environmental Protection Agency or of the Food and Drug Administration must have access to the written procedures established for the inspection and may request testing facility management to certify that inspections are being implemented, performed, documented and followed-up in accordance with this paragraph.

(v) All records maintained by the quality assurance unit must be kept in one location at the testing facility.

(d) *Facilities.* (1) *General.* Each testing facility must be of suitable size, construction, and location to facilitate the proper conduct of studies. It must be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.

(2) *Animal care facilities.* (i) A testing facility must have a sufficient number of animal rooms or areas, as needed, to assure proper:

(A) Separation of species or test systems,

(B) Isolation of individual projects,

(C) Quarantine of animals, and

(D) Routine or specialized housing of animals.

(ii) A testing facility must have a number of animal rooms or areas separate from those described in paragraph (d)(2)(i) of this section to ensure isolation of studies being done with test systems or test and control substances known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.

(iii) Separate areas must be provided for the diagnosis, treatment, and control of laboratory animal diseases. These areas must provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals.

(iv) When animals are housed, facilities must exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities must be provided and operated to minimize vermin infestation, odors, disease hazards, and environmental contamination.

(v) Animal facilities must be designed, constructed, and located so as to minimize disturbances that interfere with the study.

(vi) In addition to the requirements as described in paragraphs (d)(2)(i)–(v) of this section, more detailed guidance on animal care facilities is given in Appendix A of this section.

(3) *Animal supply facilities.* There must be storage areas for feed, bedding, supplies, and equipment. Storage areas for feed and bedding must be separated from areas housing the test systems and must be protected against infestation or contamination. Refrigeration must be provided for perishable supplies or feed.

(4) *Facilities for handling test and control substances.* (i) As necessary to prevent contamination or mixups, there must be separate areas for:

(A) Receipt and storage of the test and control substances.

(B) Mixing of the test and control substances with a carrier, e.g., feed.

(C) Storage of the test and control substance/carrier mixtures.

(ii) Storage areas for the test or control substance and test and control mixtures must be separate from areas housing the test systems and must be adequate to preserve the identity, strength, purity, and stability of the substances and mixtures.

(5) *Laboratory operation areas.* (i) Separate laboratory space must be provided for the performance of the routine procedures required by studies, including specialized areas for performing activities such as aseptic surgery, intensive care, necropsy, histology, radiography, and handling of biohazardous materials.

(ii) Separate space must be provided for cleaning, sterilizing, and maintaining equipment and supplies used during the course of the study.

(iii) In addition to the requirements described in paragraphs (d)(s)(i)–(ii) of this section, more detailed guidance on handling of radioactive materials is given in Appendix A of this section.

(6) *Specimen and data storage facilities.* Space must be provided for archives, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.

(7) *Administrative and personnel facilities.* (i) There must be space provided for the administration, supervision, and direction of the testing facility.

(ii) Separate space must be provided for locker, shower, toilet, and washing facilities.

(iii) In addition to the requirements in paragraphs (d)(7)(i)–(ii) of this section, more detailed guidance on administrative and personnel facilities is given in Appendix A of this section.

(e) *Equipment.* (1) *Equipment design.* Automatic, mechanical, or electronic equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control must be of appropriate design and adequate capacity to function according to the protocol and must be suitably located for operation, inspection, cleaning, and maintenance.

(2) *Maintenance and calibration of equipment.* (i) Equipment must be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data must be adequately tested, calibrated, and/or standardized.

(ii) The written standard operating procedures required under paragraph (f)(1) of this section must set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and must specify remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures must designate the person responsible for the performance of each operation, and copies of the standard operating procedures must be made available to laboratory personnel.

(iii) Written records must be maintained of all inspection, maintenance, testing, calibrating, and/or standardizing operations. These records, containing the date of the operation, must describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records must be kept of nonroutine repairs performed on equipment as a result of failure and malfunction. Such records must document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.

(f) *Testing facilities operation.* (1) *Standard operating procedures.* (i) A testing facility must have written standard operating procedures setting forth study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All deviations in a study from standard operating procedures must be authorized by the study director and must be documented in the raw data. Significant changes in established standard operating procedures must be properly authorized in writing by management.

(ii) Standard operating procedures must be established for, but not limited to, the following:

(A) Animal room preparation.

(B) Animal care.

(C) Receipt, identification, storage, handling, mixing, and method of sampling of the test and control substances.

(D) Test system observations.

(E) Laboratory tests.

(F) Handling of animals found moribund or dead during study.

(G) Necropsy of animals or postmortem examination of animals.

(H) Collection and identification of specimens.

(I) Histopathology.

(J) Data handling, storage, and retrieval.

(K) Maintenance and calibration of equipment.

(L) Transfer, proper placement, and identification of animals.

(iii) Each laboratory area must have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed, e.g., toxicology, histology, clinical chemistry, hematology, teratolgy, necropsy. Published literature may be used as a supplement to standard operating procedures.

(iv) A historical file of standard operating procedures, and all revisions

thereof, including the dates of such revisions, must be maintained.

(2) *Reagents and solutions.* All reagents and solutions in the laboratory areas must be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions must not be used.

(3) *Animal care.* (i) There must be standard operating procedures for the housing, feeding, handling, and care of animals.

(ii) All newly received animals from outside sources must be placed in quarantine until their health status has been evaluated and documented. This evaluation must be in accordance with acceptable veterinary medical practice.

(iii) At the initiation of a study, animals must be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals must be isolated. If necessary, hese animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment must be documented and must be retained.

(iv) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), must each receive appropriate identification (e.g., tattoo, toe clip, color code, ear tag, ear punch, etc.). All information needed to specifically identify each animal within an animal housing unit must appear on the outside of that unit.

(v) Animals of different species must be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control or test substances or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification must be made.

(vi) Animal cages, racks and accessory equipment must be cleaned and sanitized at appropriate intervals.

(vii) Feed and water used for the animals must be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses must be maintained as raw data.

(viii) Bedding used in animal cages or pens must not interfere with the purpose or conduct of the study and must be changed as often as necessary to keep the animals dry and clean.

(ix) The use of cleaning and pest control materials must be documented. Cleaning and pest control materials that interfere with the study must not be used.

(x) In addition to the requirements as described in paragraphs (f)(3) (i)–(ix) of this section, more detailed guidance for proper animal care is given in Appendix A of this section.

(g) *Protocol for and conduct of a study.* (1) *Protocol.* (i) Each study must have a sponsor-approved protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol must contain but not necessarily be limited to the following information:

(A) A descriptive title and statement of the purpose of the study.

(B) Identification of the test and control substance by name, chemical abstract (CAS) number or code number.

(c) The name and address of the sponsor including the sponsor's project manager. The name and address of the testing facility at which the study is being conducted.

(D) The proposed starting and completion dates.

(E) Justification for selection of the test system.

(F) Where applicable, the number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.

(G) The procedure for identification of the test system.

(H) A description of the study design, including the methods for control of bias.

(I) A description and/or identification of the diet used in the study as well as solvents, emulsifiers and/or other materials used to solubilize or suspend the test or control substances before mixing with the carrier. The description must include specification for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

(J) The route of administration and the reason for its choice.

(K) Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control substance to be administered and the method and frequency of administration.

(L) Method by which the degree of absorption of the test and control substances by the test system will be determined if necessary to achieve the objectives of the study.

(M) The type and frequency of tests, analyses, and measurements to be made.

(N) The records to be maintained.

(O) The date of approval of the protocol by the sponsor and the signature of the study director.

(P) A statement of the proposed statistical methods to be used.

(ii) All changes in or revisions of the sponsor approved protocol and the reasons therefore must be documented, signed by the study director, dated, and maintained with the protocol.

(iii) In addition to the protocol requirements as described in paragraphs (g)(1)(i)–(ii) of this section, additional protocol requirements will be specified in individual test standards.

(2) *Conduct of a study.* (i) The study must be conducted in accordance with the protocol.

(ii) The test systems must be monitored in conformity with the protocol.

(iii) Specimens must be identified by test system, study, nature, and date of collection. This information must be located on the specimen container or must accompany the specimen in a manner that precludes error in the recording and storage of data.

(iv) Records of gross findings for a specimen from postmortem observations must be available to a pathologist when examining that specimen histopathologically.

(v) All data generated during the conduct of a study, except those that are generated as direct computer input, must be recorded directly, promptly, and legibly in permanent ink. All data entries must be dated on the day of entry and signed or initialed by the person entering the data. Any change in entries must be made so as not to obscure the original entry, must indicate the reason for such change, and must be dated and signed or identified at the time of the change. In computer driven data collection systems, the individual responsible for direct data input must be identified at the time of data input. Any change in computer entries must be made so as not to obsure the original entry, must indicate the reason for change, and must be dated and the

responsible individual must be identified.

(h)–(i) [Reserved].

(j) *Records and reports.* (1) *Reporting of study results.* (i) A final report must be prepared for each study in accordance with the EPA reporting requirements. The reports must include, but not necessarily be limited to, the following:

(A) Name and address of the facility performing the study and the dates on which the study was initiated and completed.

(B) Objectives and procedures stated in the sponsor-approved protocol, including any changes in the original protocol including justification(s).

(C) Statistical methods employed for analyzing the data.

(D) The test and control substances identified by name, chemical abstract (CAS) number or code number, strength, purity, and composition or other appropriate characteristics.

(E) Stability of the test and control substances under the conditions of administration and storage.

(F) A description of the methods used.

(G) A description of the test system used. Where applicable, the final report must include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification.

(H) A description of the dosage, dosage regimen, route of administration, and duration.

(I) A description of all circumstances that may have affected the quality or integrity of the data.

(J) The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study.

(K) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.

(L) The signed and dated reports of each of the individual scientists or other professionals involved in the study.

(M) The locations where all specimens, raw data, and the final report are to be stored.

(N) The statement prepared and signed by the quality assurance unit as described in paragraph (c)(4)(ii)(G) of this section.

(ii) The final report must be signed by the study director.

(iii) Corrections or additions to a final report must be in the form of an amendment by the study director. The amendment must clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and must be signed and dated by the person responsible.

(iv) In addition to the Reporting requirements in paragraphs (j)(1)(i)–(iii) of this section, additional Reporting requirements will be specified in individual test standards.

(2) *Storage and retrieval of records and data.* (i) All raw data, documentation, protocols, speciments, and final reports generated as a result of a study must be retained and indexed.

(ii) There must be an archive(s) for orderly storage and expedient retrieval of all raw data, documentation, protocols, speciments, and interim and final reports. Conditions of storage must minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens. Tissue blocks must be separated from specimen slides by a fire resistant barrier. A testing facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens may be retained elsewhere provided the archive(s) have specific reference to those other locations.

(iii) An individual must be identified as responsible for the archives.

(iv) Only authorized personnel must enter the archives. Those who enter, must sign in and out, identify data removed and returned and dates removed and returned.

(v) Material retained or referred to in the archives must be indexed by test substance or mixture, date of study, test system, and nature of study.

(vi) In addition to the Stroage and Retrieval of Records and Data requirements as described in paragraphs (j)(2)(i)–(v) of this section, additional requirements will be specified in individual test standards.

(3) *Retention of records.* (i) Record retention requirements set forth in this subsection do not supercede the record retention requirements of any other regulations in this chapter.

(ii) Except as provided in paragraph (j)(3)(iii) of this section, documentation records, raw data, and specimens pertaining to a study and required to be made by this part must be retained in the archive(s) of the testing facility or sponsor for at least 10 years from the date the study is submitted to the Agency.

(iii) Wet specimens, samples of test or control substances, samples of test or control substance/carrier mixtures and specially prepared material (e.g., histochemical, electron microscopic, blood mounts, teratological preparation, and uteri from dominant lethal mutagenesis tests), which are relatively fragile and differ markedly in stability and quality during storage, must be retained only as long as the quality of the preparation affords evaluation. In no case must retention be required for a longer period than that set forth in paragraph (j)(3)(i) of this section.

(iv) The master schedule sheet, copies of protocols, and records of quality assurance inspections, as required by paragraph (c)(4)(iii) of this section must be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraph (j)(3)(ii) of this section.

(v) Summaries of training and experience and job descriptions required to be maintained by paragraph (c)(1)(i)(B) of this section must be retained along with all other testing facility employment records for the length of time specified in paragraph (j)(3)(i) of this section.

(vi) Records and reports of the maintenance and calibration and inspection of equipment, as required by paragraph (e)(2)(ii) and (iii) of this section, must be retained for the length of time specified in paragraph (j)(3)(i) of this section.

(vii) If a facility conductiong testing or an archive contracting facility goes out of business, all raw data, documentation, and other material specified in this section must be transferred to the archives of the sponsor of the study. The Agency must be notified in writing of such a transfer and its specific location. If a facility conducting testing or an archive contracting facility changes ownership or management, the Agency and the sponsor must be notified and concur with the disposition of the archives.

(k) *Inspection of a testing facility.* (1) A testing facility must permit an authorized employee of the Environmental Protection Agency or of the Food and Drug Administration, at reasonable times and in a resonable manner, to inspect the facility and to inspect (and in the case of records, also to copy) all records and specimens required to be maintained regarding studies within the scope of this section. The records inspection and copying requirements shall not apply to quality assurance unit records of findings and problems, or to action recommended and taken.

(2) The Environmental Protection Agency will not consider reliable for purposes of showing that a chemical

substance or mixture does not present a risk of injury to health or the environment any data developed by a testing facility that refuses to permit inspection. The Agency, at its discretion, may for purposes of showing adverse effects rely upon studies conducted by laboratories refusing inspection. The determination that a study will not be considered does not however, relieve the sponsor of a required test of the obligation under any applicable statute or regulation to submit the results to the Environmental Protection Agency.

Appendix A

This Appendix provides guidance on certain issues related to Good Laboratory Practices for Health Effects. Information or methods contained in this Appendix apply to all health effects studies in Part 772.

(a) *Handling of Test Substances.* To minimize possible adverse effects on the health of testing facility personnel from exposure to toxic test substances, testing facilities and personnel should use the following documents (or revisions of these documents) as guidelines for the handling of potentially toxic test substances: the DHEW Toxicology Subcommittee document for Carcinogen Standards (August 1978) entitled, "Guidelines for the Laboratory Use of Toxic Substances Posing a Potential Occupational Carcinogenic Risk," and the IARC document entitled, "A Manual on the Safety of Handling Carcinogens in the Laboratory."

(b) *Handling of Radioactive Materials.* If radioactive materials are to be used, special facilities or areas and licensing of persons to possess and use radioactive materials should be in accordance with regulations set forth by the Nuclear Regulatory Commission in Title 10 of the Code of Federal Regulations or the requirements of an agreement State.

(c) *Administrative and Personnel Facilities.* Testing facilities should be in accordance with regulations set forth by the Occupational Safety and Health Administration under Title 29 of the Code of Federal Regulations.

(d) *Animal Care and Handling.* (1) All animals under the care of the testing facility should be housed, fed, and handled in compliance with standards set forth by the Animal Welfare Act of 1970 under 9 CFR Part 3, or, where standards are not indicated in 9 CFR Part 3, animals should be housed, fed, and handled in a manner consistent with the recommendations in HEW Publication No. (NIH) 74–23, "Guide for the Care and Use of Laboratory Animals," and a report of the Committee on Long-Term Holding of Laboratory Animals," and a report of the Committee on Long-Term Holding of Laboratory Rodents (ILAR News, Vol. XIX, No. 4, 1976). All animals for which there are no specific regulations should be housed, fed, and handled in compliance with Subpart E of 9 CFR Part 3, the recommendations of HEW Publication No. (NIH) 74–23 and the National Academy of Sciences/National Research Council, "Standards for the Breeding, Care and Management of Syrian Hamsters (1960); Laboratory Mice (1962); Laboratory Rats (1962); Guinea Pigs (1964); Laboratory Cats (1964); Laboratory Dogs (1964); and Laboratory Rabbits (1965)." Should these guidelines and standards be revised, animal care should be in accordance with such revisions.

(2) Animal cages, racks and accessory equipment should be cleaned and sanitized at appropriate intervals as recommended in HEW Publication No. (NIH) 74–23 and any revision of this document.

(e) *Animal Care Facilities.* Structural requirements and environmental control of rooms or areas for animals should comply with the provisions of the Animal Welfare Act of 1970 (Pub. L. 91–579) as set forth in 9 CFR Part 3. Space requirements for the primary enclosure should also be as specified in 9 CFR Part 3, except that where specifications regarding housing of certain species of animals are not set forth in the recommendations contained in HEW Publication No. (NIH 74–23) entitled, "Guide for the Care and Use of Laboratory Animals," and a report of the Committee on Long-Term Holding of Laboratory Rodents (ILAR News, Vol. XIX, No. 4, 1976) should be followed including any revisions of these documents.

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AGENCY PUBLICATION ON ASSIGNED DAYS OF THE WEEK

The following agencies have agreed to publish all documents on two assigned days of the week (Monday/Thursday or Tuesday/Friday).

This is a voluntary program. (See OFR NOTICE FR 32914, August 6, 1976.)

Monday	Tuesday	Wednesday	Thursday	Friday
DOT/COAST GUARD	USDA/ASCS		DOT/COAST GUARD	USDA/ASCS
DOT/NHTSA	USDA/APHIS		DOT/NHTSA	USDA/APHIS
DOT/FAA	USDA/FNS		DOT/FAA	USDA/FNS
DOT/OHMO	USDA/FSQS		DOT/OHMO	USDA/FSQS
DOT/OPSO	USDA/REA		DOT/OPSO	USDA/REA
CSA	MSPB*/OPM*		CSA	MSPB*/OPM*
	LABOR			LABOR
	HEW/FDA			HEW/FDA

Documents normally scheduled for publication on a day that will be a Federal holiday will be published the next work day following the holiday.

Comments on this program are still invited. Comments should be submitted to the Day-of-the-Week Program Coordinator, Office of the Federal Register, National Archives and Records Service, General Services Administration, Washington, D.C. 20408

***NOTE: As of January 1, 1979, the Merit Systems Protection Board (MSPB) and the Office of Personnel Management (OPM) will publish on the Tuesday/Friday schedule. (MSPB and OPM are successor agencies to the Civil Service Commission.)**

REMINDERS

The items in this list were editorially compiled as an aid to Federal Register users. Inclusion or exclusion from this list has no legal significance. Since this list is intended as a reminder, it does not include effective dates that occur within 14 days of publication.

Rules Going Into Effect Today

ENVIRONMENTAL PROTECTION AGENCY

21019 4-9-79 / New Mexico Air Quality Control Act

HOUSING AND URBAN DEVELOPMENT DEPARTMENT

Office of Assistant Secretary for Community Planning and Development—

21227 4-9-79 / Comprehensive planning assistance; approval and disapproval of land use and housing element requirement (retroactive to September 5, 1978)

Office of Assistant Secretary for Neighborhoods, Voluntary Associations and Consumer Protection—

21014 4-9-79 / Mobil home procedural and enforcement regulations; extension of conditional approval time for State Administrative Agencies

NUCLEAR REGULATORY COMMISSION

26060 5-4-79 / Uranium fuel cycle impacts from spent fuel reprocessing and radioactive waste management; extension of interim fuel cycle rule to 5-15-79 (originally published at 42 FR 13803, 3-14-77)

TREASURY DEPARTMENT

Customs Service—

17653 3-23-79 / Fasteners from Japan

Next Week's Deadlines for Comments on Proposed Rules

AGRICULTURE DEPARTMENT

Agricultural Marketing Service—

25460 5-1-79 / Avocados grown in South Florida and imported avocados; grade and maturity requirements; comments by 5-17-79

Commodity Credit Corporation—

22081 4-13-79 / 1979 Crop peanut loan and purchase program; comments by 5-14-79

Farmers Home Administration—

21994 4-12-79 / Rural housing loans and grants; technical and supervisory assistance; comments by 5-14-79

Rural Electrification Administration—

14607 3-13-79 / 15 and 25 kV primary underground power cable specifications; comments by 5-14-79

COMMERCE DEPARTMENT

National Oceanic and Atmospheric Administration—

18031 3-26-79 / Stone crab fishery; energency regulations; comments by 5-19-79

19445 4-3-79 / Stone crab fishery; plan approved and proposed regulations; comments by 5-19-79

Patent and Trademark Office—

16022 3-16-79

22478 3-16-79 / Compulsory counterclaims in trademark opposition and cancellation proceedings; comments by 5-15-79 (2 documents)

COMMODITY FUTURES TRADING COMMISSION

16443 3-19-79 / Application fees for registraion with Commission to be nonrefundable; comments by 5-18-79

ENERGY DEPARTMENT

22608 4-16-79 / Weatherization assistance program provisions; comments by 5-16-79

Economic Regulatory Administration—

19423 4-3-79 / Butane and natural gasoline deregulation; comments by 5-18-79

17644 3-29-79 / Natural gas transportation certificates, displacement of fuel oil; comments by 5-17-79

20444 4-5-79 / Participation of gasoline retailers in State set-aside programs in mandatory petroleum allocation; comments by 5-15-79

Federal Energy Regulatory Commission—

22090 4-13-79

23093 4-18-79 / Determination of incentive rate of return, tariff, and related issues for the Alaska Natural Gas Transportation System; reply comments by 5-16-79 (2 documents)

22751 4-17-79 / Voluntary annual reporting of electric utility conservation activities; comments by 5-17-79

ENVIRONMENTAL PROTECTION AGENCY

22126 4-13-79 / Air pollution; approval and promulgation of nonattainment plan for S.D.; comments by 5-14-79

22130 4-13-79 / Air pollution; delayed compliance orders; North Carolina; Georgia-Pacific Corp.; comments by 5-14-79

22131 4-13-79 / Air pollution; delayed compliance orders; North Carolina; Pittsburg Plate Glass Industries; comments by 5-14-79

22129 4-13-79 / Air pollution; delayed compliance orders; North Carolina; True Temper Corp.; comments by 5-14-79

22127 4-13-79 / Air pollution; approval and promulgation of nonattainment plan for Wyo.; comments by 5-14-79

15743 3-15-79 / Attainment status designations; comments by 5-14-79

22480 4-16-79 / Disapproval of delayed compliance order issued by Wyoming Department of Environmental Quality to Black Hills Power & Light Co.; comments by 5-16-79

22752 4-17-79 / Food additive tolerances for insecticide propargite; comments by 5-17-79

23094 4-18-79 / Pesticide chemicals in or on raw agricultural commodities; tolerances for the pesticide chemical Methyl 3-[(dimethoxyphosphinyl)oxy]butenoate; comments by 5-18-79

14578 3-13-79 / Prevention of discharge of dredged or fill material into defined area waters of the U.S.; comments by 5-14-79

15742 3-15-79 / Review of performance standards for sulfuric acid plants; comments by 5-14-79

FEDERAL COMMUNICATIONS COMMISSION

19000 3-30-79 / AM stereophonic broadcasting; comments period extended to 5-15-79

[Originally published at 43 FR 48669, 10-19-78]

21831 4-12-79 / Exemption from watch requirements for Class III-B public coast stations; comments by 5-16-79

51650 11-6-78 / Television receiver noise figures, measurement techniques; reply comments by 5-15-79

FEDERAL MARITIME COMMISSION

14582 3-13-79 / Prehearing and discovery procedure improvements; comments by 5-14-79

22487 4-16-79 / Self-policing of independent liner operators; comments by 5-16-79

FEDERAL RESERVE SYSTEM

20716 4-6-79 / International banking facilities; exemption from reserve requirements and interest rate restrictions; comments by 5-18-79

23868 4-23-79 / Reserve requirements on Federal funds and repurchase agreement time deposits of member banks; comments by 5-18-79

HEALTH, EDUCATION, AND WELFARE DEPARTMENT

Food and Drug Administration—

22755 4-17-79 / Diagnostic X-Ray Systems; proposed amendment of assembly and reassembly provisions; comments by 5-17-79

22058 4-13-79 / Penicillin antibiotic drugs; penicillamine capsules and tablets; comments by 5/14/79

Health Care Financing Administration—

25476 5-1-79 / Apportionment of malpractice costs to medicare; comment period extended to 5-15-79

[First published at 44 FR 15744, 3-15-79]

15746 3-15-79 / Limitations on reimbursable costs under Medicare; comments by 5-14-79

Office of the Secretary—

16444 3-19-79 / Debarment and suspension from eligibility for financial assistance; comments by 5-18-79

HOUSING AND URBAN DEVELOPMENT DEPARTMENT

Office of Assistant Secretary for Housing—Federal Housing Commissioner—

22472 4-16-79 / Determining of utilities allowances for tenants of PHA-owned projects; comments period extended to 5-16-79

[Originally published at 44 FR 1600, Jan. 5, 1979]

22652 4-16-79 / College Housing Program for Fiscal Year 1979; loan provisions; comments by 5-16-79

22472 4-16-79 / PHA-owned projects—demolition of structures or disposition of real property; comments by 5-16-79

22472 4-16-79 / Public housing agencies; energy audits and energy conservation measures and individual metering of utilities; comments period extended to 5-16-79

[Originally published at 44 FR 60854, Dec. 28, 1978]

23093 4-18-79 / Revised prescription of design standards pursuant to the Architectural Barriers Act of 1968; comments by 5-18-79

INTERIOR DEPARTMENT

Land Management Bureau—

16800 3-19-79 / Management of Federally-owned coal through lease or exchange; comments by 5-18-79

JUSTICE DEPARTMENT

Immigration and Naturalization Service—

14562 3-13-79 / Indus, Minn.; closing of port; comments by 5-14-79

LEGAL SERVICES CORPORATION

22482 4-16-79 / Rehabilitation funding provisions; comments by 5-16-79

NATIONAL CREDIT UNION ADMINISTRATION

20447 4-5-79 / Organization and operation of Federal Credit Unions; comments by 5-15-79

NUCLEAR REGULATORY COMMISSION

18513 3-28-79 / Nuclear power reactors, fracture toughness requirements; comments by 5-14-79

PENNSYLVANIA AVENUE DEVELOPMENT CORPORATION

22061 4-13-79 / Planning and design objectives, controls, and standards on Square 291; comments by 5-14-79

PERSONNEL MANAGEMENT OFFICE

19974 4-3-79 / Post employment conflict of interest; interim regulations; comments by 5-18-79

SECURITIES AND EXCHANGE COMMISSION

16935 3-20-79 / Investment company sales literature interpretative rule; comments by 5-15-79

TRANSPORTATION DEPARTMENT

Federal Aviation Administration—

15732 3-15-79 / Radiation surveys of airport X-Ray inspection cabinets; comments by 5-14-79

TREASURY DEPARTMENT

Comptroller of the Currency—

15728 3-15-79 / Foreign banks at Federal branches and agencies, national banking law applicability; comments by 5-14-79

Next Week's Meetings

ACCIDENT AT THREE MILE ISLAND, PRESIDENT'S COMMISSION

25961 5-3-79 / Middletown, Pa. (open), 5-17 through 5-19-79

AGING, FEDERAL COUNCIL

24637 4-26-79 / Washington, D.C. (open), 5-15-79

AGRICULTURE DEPARTMENT

Forest Service—

21057 4-9-79 / Coconino National Forest Grazing Advisory Board, Flagstaff, Ariz. (open), 5-15-79

19497 4-3-79 / Modoc National Forest Grazing Advisory Board, Alturas, Calif. (open), 5-16-79

Science and Education Administration—

25895 5–3–79 / Cooperative Forestry Research Advisory Board and Advisory Committee, St. Paul, Minn. (open),5–15, 5–16, and 5–17–79

CIVIL RIGHTS COMMISSION

23270 4–19–79 / Missouri Advisory Committee, St. Louis, Mo. (open), 5–18–79

20735 4–6–79 / New York Advisory Committee, Schenectady, N.Y. (open), 5–18 and 5–19–79

25657 5–2–79 / North Carolina Advisory Committee, Raleigh, N.C. (open), 5–18–79

23271 4–19–79 / Vermont Advisory Committee, Montpelier, Vt. (open), 5–15–79

COMMERCE DEPARTMENT

Industry and Trade Administration—

25487 5–1–79 / Computer Systems Technical Advisory Committee and Computer Peripherals, Components and Related Test Equipment Technical Advisory Committee, Washington, D.C. (partially open), 5–17–79

25260 4–30–79 / Foreign Availability Subcommittee of the Computers Systems Technical Advisory Committee, Washington, D.C. (open), 5–15–79

25260 4–30–79 / Hardware Subcommittee of the Computer Systems Technical Advisory Committee, Washington, D.C. (partially open), 5–16–79

25261 4–30–79 / Licensing Procedures Subcommittee of the Computer Systems Technical Advisory Committee, Washington, D.C. (open), 5–15–79

25261 4–30–79 / Memory and Media Subcommittee of the Computer Peripherals, Components, and Related Test Equipment Technical Advisory Committee, Washington, D.C. (partially open), 5–16–79

National Oceanic and Atmospheric Administration—

25262 4–30–79 / Coastal Zone Management Advisory Committee, New Orleans, La. (open), 5–16 through 5–18–79

24617 4–26–79 / Gulf of Mexico Fishery Management Council's Billfishes Advisory Subpanel, Tampa, Fla. (open), 5–14–79

24617 4–26–79 / Gulf of Mexico Fishery Management Council's Scientific and Statistical Committee (open), Metairie, La., 5–16 through 5–18–79

24617 4–26–79 / Gulf of Mexico Fishery Management Council's Sharks Advisory Subpanel, Metairie, La. (open), 5–15–79

25263 4–30–79 / New England Fishery Management Council, Portland, Me. (open), 5–16 and 5–17–79

CONSUMER PRODUCT SAFETY COMMISSION

24903 4–27–79 / National Advisory Committee for the Flammable Fabric Act, Washington, D.C. (open), 5–14 and 5–15–79

DEFENSE DEPARTMENT

Air Force Department—

23107 4–18–79 / USAF Scientific Advisory Board, Los Angeles, Calif. (closed), 5–14 through 5–16–79

24907 4–27–79 / USAF Scientific Advisory Board, El Segundo, Calif. (closed), 5–14 and 5–15–79

Army Department—

23555 4–20–79 / Army Science Board, Washington, D.C. (closed), 5–15 and 5–16–79

23555 4–20–79 / U.S. Army Medical Research and Development Advisory Panel Ad Hoc Study Group on Clinical and Preclinical Pharmacology, Washington, D.C. (partially open), 5–14–79

Defense Communications Agency—

23273 4–19–79 / Scientific Advisory Group, Arlington, Va. (closed), 5–17 and 5–18–79

Navy Department—

24625 4–26–79 / Resale System Advisory Committee, New Orleans, La. (partially open), 5–14–79

Office of the Secretary—

20744 4–6–79 / Advisory Group on Electron Devices, New York, N.Y. (closed), 5–16 and 5–17–79

21322 4–10–79 / Defense Intelligence School Panel of National Defense University and the Defense Intelligence School, Washington, D.C. (partially open), 5–15 through 5–17–79

22799 4–17–79 / Defense Science Board Task Force on High Energy Lasers, Washington, D.C. (closed), 5–17 and 5–18–79

17202 3–21–79 / Department of Defense Wage Committee, Alexandria, Va. (closed), 5–15–79

ENERGY DEPARTMENT

Office of the Secretary—

24340 4–25–79 / Committee on U.S. Petroleum Inventories, and Storage and Transportation Capacities; Inventory and Storage Task Group, Washington, D.C. (open), 5–17–79

FEDERAL COMMUNICATIONS COMMISSION

25508 5–1–79 / Radio Technical Commission for Marine Services; Special Committee No. 70, Washington, D.C. (open), 5–16–79

FEDERAL PREVAILING RATE ADVISORY COMMITTEE

22812 4–17–79 / Washington, D.C. (open), 5–17–79

HEALTH, EDUCATION, AND WELFARE DEPARTMENT

Disease Control Center—

24931 4–27–79 / Workshop on Occupational Health Engineering Control Technology, Cincinnati, Ohio (open), 5–16 and 5–17–79

Education Office—

24347 4–25–79 / Extension and Continuing Education National Advisory Council, Washington, D.C. (open), 5–15–79

24936 4–27–79 / National Advisory Council on the Education of Disadvantaged Children, Portland, Oreg. (open), 5–18 and 5–19–79

Food and Drug Administration—

26166 5–4–79 / Consumer Participation, New York, N.Y. (open), 5–15–79

22814 4–17–79 / Obstetrics-Gynecology Devices Section of the Obstetrics-Gynecology and Radiologic Devices Panel, Silver Spring, Md. (open), 5–14–79

22812 4–17–79 / Ophthalmic Devices Section of the Ophthalmic; Ear, Nose, and Throat; and Dental Devices Panel, Washington, D.C. (partially open) 5–14–79; (open) 5–15–79

Health Resources Administration—

23320 4–19–79 / National Advisory Council on Health Professions Education, Hyattsville, Md. (partially open), 5–14 through 5–16–79

Health Services Administration—

23320 4–19–79 / Maternal and Child Health Research Grants Review Committee, Rockville, Md. (partially open), 5–16 through 5–18–79

National Institute of Education—

25702 5–2–79 / Laboratory and Center Operations Review Panel, Washington, D.C. (open), 5–18 and 5–19–79

National Institutes of Health—

19541 4–3–79 / Arthritis, Metabolism, and Digestive Diseases National Advisory Council, Bethesda, Md. (partially open), 5–17 and 5–18–79

24237 4–24–79 / Artificial Kidney—Chronic Uremia Advisory Committee, Bethesda, Md. (open), 5–15 through 5–17–79 (Originally published at 44 FR 21079, 4–9–79)

21080 4–9–79 / Cancer Research Manpower Committee, New Orleans, La. (partially open), 5–13–79

19539 4-3-79 / Child Health and Human Development National Advisory Council, Bethesda, Md. (partially open), 5-14 and 5-15-79

19540 4-3-79 / Neurological and Communicative Disorders and Stroke National Advisory Council, Planning Subcommittee, Bethesda, Md. (partially open), 5-14-79

Office of the Secretary—

26168 5-4-79 / Fund for the Improvement of Postsecondary Education Board of Advisory, Elkridge, Md. (closed), 5-17 through 5-19-79

23321 4-19-79 / President's Committee on Mental Retardation, San Diego, Calif. (open), 5-15 through 5-17-79

24232 4-24-79 / Rights and Responsibilities of Women, Secretary's Advisory Committee, Washington, D.C. (open), 5-17 and 5-18-79

INTERIOR DEPARTMENT

Land Management Bureau—

24942 4-27-79 / California Desert Conservation Area Advisory Committee, Palm Springs, Calif. (open), 5-17 and 5-18-79

21084 4-9-79 / Casper District Grazing Advisory Board, Casper, Wyo. (open), 5-14-79

15792 3-22-79 / Colorado wilderness inventory, open house, Craig, Colo. (open), 5-15-79

17592 3-22-79 / Colorado wilderness inventory, open house, Grand Junction, Colo. (open), 5-16-79

24644 4-26-79 / Public lands in Nevada, open house, Battle Mountain, Nev., 5-14-79

24644 4-26-79 / Public lands in Nevada, open house, Ely, Nev., 5-18-79

24644 4-26-79 / Public lands in Nevada, open house, Tonopah, Nev., 5-14-79

24644 4-26-79 / Public lands in Nevada, open house, Yerington, Nev., 5-16-79

22202 4-13-79 / Shoshone District Grazing Advisory Board, Shoshone, Idaho (open), 5-16-79

National Park Service—

21716 4-11-79 / Committee for the Preservation of the White House, Washington, D.C. (open), 5-18-79

Surface Mining Reclamation and Enforcement Office—

25277 4-30-79 / Advisory Committee on Mining and Mineral Resources Research, Washington, D.C. (open), 5-15-79

INTERSTATE COMMERCE COMMISSION

25457 5-1-79 / Revisions to preliminary report of number of employees of Class I railroads, and monthly Report of Employees, Service and Compensation, forms A and B, Washington, D.C. (open), 5-15-79

JUSTICE DEPARTMENT

25952 5-3-79 / Juvenile Justice and Delinquency Prevention National Advisory Committee, Boston, Mass. (open), 5-16 through 5-19-79

LABOR DEPARTMENT

Labor Statistics Bureau—

24959 4-27-79 / Business Research Advisory Council, Washington, D.C. (open), 5-16-79

21385 4-10-79 / Price Indexes Committee of the Business Research Advisory Council, Washington, D.C. (open), 5-15-79

21385 4-10-79 / Wages and Industrial Relations Committee of the Business Research Advisory Council, Washington, D.C.(open), 5-15-79

Occupational Safety and Health Administration—

24959 4-27-79 / Construction Safety and Health Advisory Committee, Harvey, Ill. (open), 5-16 and 5-17-79

MARINE MAMMAL COMMISSION

24353 4-25-79 / Marine Mammal Commission and Committee of Scientific Advisors on Marine Mammals, San Diego, Calif. (partially open), 5-17 through 5-19-79

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

23134 4-18-79 / NASA Advisory Council (NAC), Historical Advisory Committee (open), 5-14-79

NATIONAL SCIENCE FOUNDATION

24653 4-26-79 / Advisory Committee for Behavioral and Neural Sciences, Subcommittee on Linguistics, Washington, D.C. (open and closed), 5-13 through 5-15-79

24652 4-26-79 / Advisory Committee for Behavioral and Neural Sciences, Subcommittee on Psychobiology, Washington, D.C. (open and closed), 5-16 through 5-18-79

24652 4-26-79 / Advisory Committee for Chemistry, Washington, D.C. (open and closed), 5-14 and 5-15-79

24652 4-26-79 / Advisory Committee for Physiology, Cellular, and Molecular Biology, Subcommittee on Human Cell Biology, Washington, D.C. (closed), 5-18-79

24653 4-26-79 / Advisory Committee for Social Sciences, Subcommittee on History and Philosophy of Science, Washington, D.C. (open and closed), 5-18 and 5-19-79

25710 5-2-79 / DOE/NSF Nuclear Science Advisory Committee 1979 Instrumentation Subcommittee, Washington, D.C. (open), 5-19 and 5-20-79

25710 5-2-79 / International Programs Advisory Committee, Washington, D.C. (closed), 5-18-79

OCEANS AND ATMOSPHERE NATIONAL ADVISORY COMMITTEE

25707 5-2-79 / Meeting, Kingston, R.I. (open), 5-17 and 5-18-79

SMALL BUSINESS ADMINISTRATION

21723 4-11-79 / Region VII Advisory Council, Des Mones, Iowa (open), 5-14-79

STATE DEPARTMENT

Office of the Secretary—

25962 5-3-79 / Law of the Sea Advisory Committee, Washington, D.C. (partially open), 5-18 and 5-21-79

21724 4-11-79 / Shipping Coordinating Committee, Committee on Ocean Dumping, Washington, D.C. (open), 5-15-79

24672 4-26-79 / Shipping Coordinating Committee, Subcommittee on Safety of Life at Sea, Washington, D.C. (open), 5-17-79

25552 5-1-79 / Shipping Coordinating Committee, Subcommittee on Safety of Life at Sea, Washington, D.C. (open), 5-17-79

TRANSPORTATION DEPARTMENT

Coast Guard—

22542 4-16-79 / National Boating Safety Advisory Council, Placida, Fla. (open), 5-15 and 5-16-79

Federal Aviation Administration—

21926 4-12-79 / Informal airspace meeting, Portland, Oreg. (open), 5-17-79

21926 4-12-79 / Informal airspace meeting, Seattle, Wash. (open), 5-15-79

21926 4-12-79 / Informal airspace meeting, Spokane, Wash. 5-16-79

23402 4-19-79 / Pittsburgh, Pa. terminal control area, Coraopolis, Pa. (open), 5-16-79

23401 4-19-79 / Proposed terminal area, Atlanta, Ga., 5-17-79

21927 4-12-79 / Radio Technical Commission for Aeronautics Separation Study Review Group, Washington, D.C. (open), 5-15 and 5-16-79

Federal Highway Administration—

15630 3-14-79 / Highway beautification program, Washington, D.C. (open), 5-15-79

National Highway Traffic Safety Administration—

25282 4–30–79 / Biomechanics Advisory Committee, Washington, D.C. (open), 5–15 and 5–16–79

[Originally published at 44 FR 15823, Mar. 15, 1979]

15822 3–15–79 / Regional Child Restraint Workshops, San Antionio, Tex. (open), 5–14 and 5–15–79

TREASURY DEPARTMENT

Office of the Secretary—

24681 4–26–79 / Tax Court Nominating Commission, Washington, D.C. (closed), 5–17–79

VETERANS ADMINISTRATION

17251 3–21–79 / Wage Committee, Washington, D.C., 5–17–79

WORLD HUNGER, PRESIDENTIAL COMMISSION

24661 4–26–79 / International Policy Subcommittee, New York, N.Y. (open), 5–18–79

Next Week's Public Hearings

AGING, FEDERAL COUNCIL

23124 4–18–79 / Special Aging Populations Committee, Jackson, Miss., 5–14–79

CIVIL RIGHTS COMMISSION

22139 4–13–79 / Legal developments, Washington, D.C., 5–14–79

COMMERCE DEPARTMENT

National Oceanic and Atmospheric Administration—

25484 5–1–79 / New England Fishery Management Council; Atlantic Groundfish (Cod, Haddock, and Yellowtail Flounder), Portland, Me., 5–16–79

Office of the Secretary—

24624 4–26–79 / East and West Flower Gardens; on environmental impact statement, Lake Charles, La., 5–17–79

24624 4–26–79 / East and West Flower Gardens; on environmental impact statement, Galveston, Tex., 5–18–79

ENERGY DEPARTMENT

24800 4–26–79 / Federal energy management and planning programs, San Francisco, Calif., 5–18–79

21654 4–11–79 / Residential conservation service, Denver, Colo., 5–14–79

21654 4–11–79 / Residential Conservation Service Program, Seattle, Wash., 5–17–79

16546 3–19–79 / Residential Conservation Service Program, Salt Lake, City, Utah, 5–14 through 5–16–79

Economic Regulatory Administration—

22022 4–12–79 / Electric utilities, assistance and intervention in State regulatory proceeding, Denver, Colo., 5–17–79

18856 3–29–79 / Financial assistance programs for State utility regulatory commissions and eligible nonregulated electric utilities, Denver, Colo., 5–16–79

18448 3–27–79 / Grants for Officers of Consumer Services, Denver, Colo., 5–15–79

22974 4–17–79 / Submission of reports to DOE by State regulatory authorities and nonregulated electric and gas utilities, Denver, Colo., 5–17–79

ENVIRONMENTAL PROTECTION AGENCY

22807 4–17–79 / California State motor vehicle pollution control standards, San Francisco, Calif., 5–17 and 5–18–79

[Rescheduled at 44 FR 23575, 4–20–79]

22131 4–13–79 / Gaseous emissions regulations for 1983 and later model year heavy duty engines, Ann Arbor, Mich., 5–14 and 5–15–79

18138 3–26–79 / Land fill disposal of solid waste; Washington, D.C., 5–15–79 and Houston, Tex., 5–17–79

INTERIOR DEPARTMENT

Office of the Secretary—

22823 4–17–79 / Proposed Central Utah project municipal and industrial system, Herber City, Utah, 5–17–79

22823 4–17–79 / Proposed Central Utah project municipal and industrial system, Orem, Utah, 5–19–79

22823 4–17–79 / Proposed Central Utah project municipal and industrial system, Salt Lake City, Utah, 5–18–79

INTERNATIONAL TRADE COMMISSION

25940 5–3–79 / Carbon Steel Plate from Poland; Washington, D.C., 5–24–79

JUSTICE DEPARTMENT

Law Enforcement Assistance Administration—

25527 5–1–79 / MAC Crime Prevention and Education Program, Inc., Milwaukee, Wis., 5–14 and 5–15–79

LABOR DEPARTMENT

Mine Safety and Health Administration—

23544 4–20–79 / Loading of explosives into blast holes through drill steel or other devices, Miami, Fla., 5–18–79

POSTAL RATE COMMISSION

12306 3–6–79 / Express mail metro service, 1978, Washington, D.C., 5–18–79

Documents Relating to Federal Grants Programs

This is a list of documents relating to Federal grants programs which were published in the Federal Register during the previous week.

DEADLINES FOR COMMENTS ON PROPOSED RULES

26298 5–4–79 / HEW/OE—Direct grant programs, State-administerd programs, and geneal administrative regulations; comments by 7–3–79; workshops and hearings 5–17, 6–4 through 6–8–79, and 6–11–79

APPLICATIONS DEADLINES

25694 5–2–79 / HEW/HDSO—Child welfare research and demonstration grant program for demonstration projects to assess State's foster family services systems; apply by 7–2–79 for FY 1979 grant funds, and by 1–30–80 for FY 1980 grant funds

25696 5–2–79 / HEW/HDSO Child welfare research and demonstration grant program for projects to demonstrate the planning and initiation of a comprehensive emergency services program; apply by 7–2–79 for FY 1979 grant funds, and by 1–30–80 for FY 1980 grant funds

25511 5–1–79 / HEW/HDSO—Regional adoption resources centers demonstration program—Announcement No. 13652–791; apply by 7–16–79

25821 5–2–79 / HEW/OE—Citizen education for cultural understanding program awards; apply by 6–18–79

MEETINGS

25895 5–3–79 / Commerce/NOAA—Sea Grant Review Panel, Rockville, Md. (open), 5–30 and 5–31–79

26168 5–4–79 / HEW—Board of Advisors to the Fund for the Improvement of Postsecondary Education (closed), 5–17 through 5–19–79

25709 5–2–79 / NSF—Mathematical and Computer Sciences Advisory Committee; Computer Science Subcommittee, Washington, D.C. (partially open), 5–21 through 5–23–79

25708 5–2–79 / NSF—Memory and Cognitive Processes Subcommittee, Washington, D.C. (closed), 5–21 and 5–22–79

25709 5–2–79 / NSF—Molecular Biology Subcommittee, Washington, D.C. (closed), 5–21 and 5–22–79

25708 5–2–79 / NSF—Molecular Biology Subcommittee, Washington, D.C. (closed), 5–24 and 5–25–79

25707 5-2-79 / NSF—Physiology, Cellular, and Molecular Biology Advisory Committee; Cell Biology Subcommittee, Washington, D.C. (closed), 5-21 through 5-23-79

25708 5-2-79 / NSF—Physiology, Cellular, and Molecular Biology Advisory Committee; Genetic Biology Subcommittee, Washington, D.C. (closed), 5-24 through 5-26-79

25709 5-2-79 / NSF—Sensory Physiology and Perception Subcommittee, Washington, D.C. (closed), 5-23 and 5-24-79

25709 5-2-79 / NSF—Social Sciences Advisory Committee; Geography and Regional Science Subcommittee, Washington, D.C. (closed), 5-21-79

25708 5-2-79 / NSF—Sociology Subcommittee, Washington, D.C. (closed), 5-24 and 5-25-79

OTHER ITEMS OF INTEREST

26067 5-4-79 / DOE/FERC—Time limit for Commission action on research, development and demonstration programs

25812 5-2-79 / EPA—Grants for construction of publicly-owned treatment works; protests of grantee procurement actions; subject index list of regional administrator protest determinations issued during 1978, republication

[Originally published at 44 FR 20283, April 4, 1979]

25476 5-1-79 / HEW/CDC—Comprehensive Public Health Services; decision to develop health incentive grants regulations

25820 5-2-79 / HEW/OE—Citizen education for cultural understanding program

25476 5-1-79 / HEW/PHS—Preventive Health Service Programs; intention to develop regulations on formula grants

25534 5-1-79 / LSC—Consideration of grant applications submitted by various legal service agencies (2 documents)

25706 5-2-79 / LSC—Grants and contracts; California; comments invited

25706 5-2-79 / LSC—Grants and contracts; North Carolina; comments invited

List of Public Laws

Note: No public bills which have become law were received by the Office of the Federal Register for inclusion in today's List of Public Laws.

Last Listing Apr. 12, 1979